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SPONTANEOUS MEDIASTINAL EMPHYSEMA[1]

LOUIS HAMMAN, M.D.

From the Department of Medicine, The Johns Hopkins Medical School

I am acutely sensible to the honor and distinction conferred upon me by the invitation to give the second Henry Sewall Lecture in Medicine. Last year Dr. Florence R. Sabin, inaugurating this lectureship, briefly reviewed the professional career of Dr. Sewall, traced the development of his interests through successive publications, and gave an appreciation of his work and influence. Upon this topic, happily, nothing further need be said. It was my good fortune to have known Dr. Sewall, to have met him on many occasions, and to have had pleasant and stimulating conversations with him. It was my misfortune not to have had the opportunity to know him better, and I envy the many here who daily associated with him, enjoying the charm of his genial personality; who were encouraged by his enthusiasm and stimulated by the originality and perspicuity of his vigorous mind.

On this occasion, the first clinical lecture under the foundation, you have the right to expect that your guest, so signally honored, should come prepared to tell you the significant results of some original investigation or at least to propose, upon the basis of lately won knowledge, a rearrangement of our ideas about some disease into a new and more fruitful clinical pattern. What must be your astonishment when now I invite you to go back with me a hundred years and consider matters which would have been novel and absorbing to physicians practicing at that time? The interests of physicians vary from age to age. Following Laennec's discoveries they centered upon auscultation and percussion; at the middle of the past century upon the correlation between clinical diagnosis and pathological anatomy; during the final quarter of the century upon the brilliant discoveries of the new science of bacteriology; during the past thirty years upon

[1] The Henry Sewall Lecture in Medicine. Delivered at Denver, Colorado, February 16, 1938.

pathological physiology and the intimate details of function revealed by mechanical instruments of precision and the application of the latest methods of physical and chemical research. When the abundant yield of fresh information which always follows upon the introduction of a new method of investigation begins to slaken, then interest and attention lag and eagerly turn to exploit new fields. The accumulated knowledge won by ingenuity and untiring labor during each period becomes the precious possession of the next and slowly is incorporated into the routine of daily practice. We do not lack in appreciation of the revolutionary discoveries of Laennec nor do we regard his labors as in any way inferior to the chemical and physiological studies now being so assiduously pursued. Nevertheless, they do not excite our imagination with the prospect of adventure and discovery, for the intellectual country opened by Laennec has now been thorougly explored and charted. What has been amassed is a confirmed body of fact, to be taught, and learned, and practiced as the very foundation of our art. It is inconceivable that any important new discovery will be made in this field. However, in the course of our daily practice, it must happen now and again that some hitherto unnoticed detail will come to light. Such a detail I wish now to call to your attention. In doing so I draw some comfort from the reflection that although Dr. Sewall was a trained physiologist yet he was also a practicing physician and ever keenly alive to any observation, however modest it might be, that added something to our vast store of clinical knowledge and experience. Therefore, I am encouraged to believe that Dr. Sewall, were he here, would be entertained and interested by this simple narrative of a clinical adventure.

Case 1. On February 12, 1933, Dr. W. Cabell Moore invited me to come to Washington to see a physician, fifty-one years of age, who had had symptoms strongly suggesting the occurrence of coronary occlusion. Theretofore he had always been a robust, healthy man busily engaged in carrying on an exacting practice. On the morning of February 8, while shaving, he was suddenly seized with intense pain under the sternum radiating to the left shoulder. The pain lasted about half an hour and then gradually passed. When Dr. Moore examined him two hours later no definite abnormality

was found. The heart and lungs were quite normal. The temperature was 98°; pulse, 54 and regular; respirations, 20; blood pressure, systolic 110, diastolic 80. An electrocardiogram, taken the next day, was reported by Dr. J. W. Esler as follows: "Regular rhythm; rate 60; T-waves upright in all leads; conduction interval normal; maximum QRS potential 9 mm." The blood count was normal; the leukocytes 8,500 per cubic mm. On the morning of of February 11, the patient reported to Dr. Moore that during the evening before, when lying on the left side, he had heard a curious loud bubbling, crackling sound synchronous with the heart beat. His wife, sitting on the bed beside him, had heard the sound very plainly. At this time Dr. Moore could make out no abnormality whatsoever on physical examination. The heart and lungs were quite normal. The temperature was 98°; pulse, 66; respirations 20; blood pressure, systolic 100, diastolic 75. Later in the day Dr. Esler heard the sound and interpreted it to be a pericardial friction. This seemed to confirm the diagnosis of coronary occlusion which, very naturally under the circumstances, had already been proposed. When I saw the patient on the afternoon of the following day he was sitting up in bed laughing and talking, protesting that he felt perfectly well. He certainly was in good spirits and had every appearance of robust health. The temperature, pulse, respirations and blood pressure were all normal as they had been before. I examined the heart and the lungs with the greatest care and could detect nothing that was to the least degree abnormal. When I expressed chagrin at my lack of skill, the patient laughingly said that he could easily bring on the sound which had excited so much interest. He turned on his left side and after shifting about for a few moments said, "There it is, I hear it now." I put my stethoscope over the apex of the heart and with each impulse there occurred the most extraordinary crunching, bubbling sound. It is difficult to describe. Crunching is the best adjective I can think of though it is far from apt, especially since crunching has been widely used to describe pleural friction, to which it bore no resemblance. It certainly conveyed the impression of air being churned or squeezed about in the tissues. When the patient turned on his back the sound at once disappeared. The possibility of pneumothorax came to my

mind. However, a second thorough examination of the lungs was quite negative. Still I persisted and suggested that it might be a small localized pneumothorax near the apex of the heart. The following day a roentgenogram was taken with a portable apparatus. Dr. E. M. McPeak's report reads as follows: "Examination of the chest shows the bony thorax, heart and great vessels to be normal in appearance. There is slight thickening of the interlobar pleura on the right side with some slight increase in density throughout the right base. The appearance in the right base is probably due to bronchiectasis. There is no other evidence of abnormality except perhaps a very slight widening of the aortic arch and the thoracic aorta."

The extraordinary sound disappeared after a few days. At the end of two weeks the patient was up and about and during the past five years has led an active life and has remained well.

This experience left me greatly puzzled. Although the character and intensity of the pain was like that of coronary occlusion, still, the fact that when the pain had gone the patient felt perfectly well and had none of the constitutional symptoms and other manifestations of shock, which are such typical features of this condition, convinced me that he did not have coronary occlusion. Moreover, the peculiar sound heard over the heart did not have the distinctive features of a pericardial rub, nor did the patient have the pain and fever which almost certainly would have accompanied a pericarditis sufficiently pronounced to have caused such a decided friction. Therefore, after the symptoms had disappeared, I did not hesitate to advise that the patient be allowed to leave the bed and slowly resume his accustomed activities.

None the less, I could offer no reasonable interpretation of the remarkable sound heard over the heart. Never before had I heard such a sound. It was an unpleasantly bewildering experience and almost daily I revolved the problem in my mind seeking an adequate solution, until four months later, when I heard precisely the same sound over the heart of a boy under circumstances which left no doubt as to the way it was produced, and clearly explained the nature and meaning of the symptoms I had observed in the Washington physician.

Case 2. A white boy, seventeen years of age, a tin-worker, was admitted to the Johns Hopkins Hospital (*History No. 49976*) June 25, 1933, complaining of pain under the sternum and swelling above the clavicles. On the previous afternoon while sitting quietly in a chair, he suddenly had a feeling of pressure under the sternum as though a lump were forming. Soon swelling actually appeared above the clavicles and he had severe pain on breathing deeply, on swallowing and on turning the head. All of that night he was very uncomfortable, spending most of the time sitting up. The next morning he entered the hospital. He was a thin, pale, undernourished lad lying quietly in bed complaining of pain under the sternum and about the neck. He was mildly apprehensive. There was subcutaneous crepitation over the front of the neck which extended backward to the trapezius muscle on both sides and downward over the clavicles to about the second rib on the left and to the nipple on the right. When I put my stethoscope over the heart, there was the same systolic crunching sound which had so perplexed me when I heard it over the heart of the Washington physician. For two days there was a little fever, the temperature on one occasion reaching 101.2°. The leucocyte count was 13,000. The roentgenogram demonstrated the presence of air in the mediastinal tissues between the heart and the anterior wall of the chest and in the subcutaneous tissues of the neck. The symptoms soon subsided, and the subcutaneous emphysema and the curious sound over the heart disappeared. Four weeks later the patient reported at the Out-Patient Clinic. He was feeling perfectly well, the physical examination was quite negative, and the roentgenogram was normal.

The facts concerning this case I transmitted at once to Dr. Moore, very delighted that at last I could explain the mechanism of the pain and of the curious sound heard over the heart of the patient we had seen together. Fortunately, the following spring Dr. Moore observed a case which fully convinced him that the explanation I had found was the correct one. I am indebted to Dr. C. R. Huffman for a summary of the records of this patient.

Case 3. A young physician, twenty-five years of age, an interne at the Emergency Hospital, Washington, was admitted as a patient, February 21, 1934, complaining of pain in the left side of the chest

and a peculiar crackling noise in the region of the heart. He had had a slight cold for two or three weeks with a little cough and mucoid expectoration. On the day before entering the hospital he had had rather sharp pain over the heart increased by deep breathing and by coughing. A few hours later as he was leaning upon his desk, he suddenly heard a curious crackling noise, apparently coming from that part of the chest where the pain was located. He listened with interest and observed that the crackling sound came synchronously with the heart beat. When he sat up straight the sound immediately vanished.

He was a well nourished man of healthy appearance. The lungs were clear except for a few transient fine rales in the interscapular area. The heart was not enlarged, the sounds were clear and of normal quality. When the patient turned upon his left side a curious moist crepitant, or crackling, noise was heard with each contraction of the heart, so loud that through the stethoscope it was almost painful to the ear. It could be heard by the bare ear held a foot from the chest wall. When the patient turned upon his back these peculiar sounds at once disappeared.

The patient remained in the hospital ten days during which time his temperature did not exceed 99.4°. The leucocyte count was normal. After the fifth day the crackling sounds over the heart could be heard only with difficulty; on the eighth day they disappeared entirely. A roentgenogram of the chest was reported to be normal. After a few weeks the patient returned to work and since then has remained well.

I was now convinced that the symptoms of these three patients had been due to the escape of air into the interstitial tissue of the lungs, the air quickly reaching the mediastinum; and that in at least certain instances this condition could be diagnosed only by hearing a very unusual crunching or crackling sound over the heart, synchronous with each contraction. I was eager for an opportunity to display this freshly won knowledge but the opportunity did not come until the spring of 1935.

Case 4. On May 18, 1935, I saw with Dr. T. F. Leitz, at the Union Memorial Hospital, Baltimore, a young man, thirty-four years of age. On the afternoon of the preceding day he had motored from New

York to Wilmington, arriving there at about seven o'clock in the evening. As he got out of the car he was taken suddenly with a very severe pain under the lower end of the sternum and a sensation of pressure or choking. Thinking the symptoms were due to indigestion he took several large doses of soda. The pain continued severely for about two hours. At the end of this time the soda began to act as a laxative and he had two or three copious watery stools. After this the pain in the chest was greatly relieved and he was able to go to the house of friends and there spend the evening. At about ten o'clock he became aware of a curious sensation over the heart, which he spoke of as a fluttering although when he felt his pulse it was beating quietly and regularly. He was quite sure that at the time of the fluttering he heard a peculiar noise coming from the region of the heart and when he put his hand over the heart he felt a vibration. This sensation of fluttering accompanied by the odd sound recurred at intervals. At midnight he boarded the train for the South. When he attempted to lie down in his berth the pain became excruciatingly severe and he was obliged at once to sit up. The pain radiated to the shoulders and down the left arm. He grew very alarmed about his condition and feared he might be dying. He alighted from the train at Baltimore, went to a hotel, and Dr. Leitz was hurriedly summoned. When Dr. Leitz arrived the patient looked to be very ill and after hearing the story Dr. Leitz took him at once to the hospital. There he was given an injection of morphia and soon fell asleep.

I saw the patient at noon on May 18. He had been dozing and was still a little dull from the morphia. When aroused he laughed, seemed unconcerned and talked freely about his experience. He said he was comfortable so long as he lay perfectly still but as soon as he twisted about the pain returned. He was a very thin man of extreme enteroptotic build. His color was good, the pulse slow and regular and he did not seem to be at all ill. The physical examination was quite negative; the lungs clear, the heart sounds of normal quality. While the patient was lying flat upon his back, just inside the apex-beat, could be heard a queer crackling, bubbling sound with each systole. When he turned upon his side the sound disappeared.

The patient remained in the hospital two weeks. After the first

day he was quite comfortable. The peculiar systolic sound at the apex of the heart disappeared on the second day. He had no fever. The leucocyte count was normal. A roentgenogram taken the day after admission showed a small pneumothorax at the left apex. An electrocardiogram taken shortly after admission showed low voltage in the first lead and biphasic T-waves in the second lead.

Subsequent roentgenograms demonstrated the presence of small areas of soft infiltration at the apices of both lungs. There were no symptoms of active tuberculosis but as a precaution the patient spent a few months at Saranac Lake under the care of Dr. Lawrason Brown. In July 1936 he had an attack of spontaneous pneumothorax. During this attack he was under the care of Dr. L. B. Flynn of Wilmington who reports upon the condition as follows:

"On the evening of July 19th I received a telephone message from Mr. C. that he though he had another attack of pneumothorax. I saw him about midnight. His symptoms were mild but he was very apprehensive. Examination at that time revealed some diminution of breath sounds over the left upper chest. The following day the physical signs were more pronounced. There was no shift of the mediastinum. No change in the pulse rate, and no fever. Three days later, under the fluoroscope, a partial collapse of the left upper lobe was clearly visible. Mr. C. stayed in bed for about two weeks and at the end of that time examination no longer showed any evidence of pneumothorax. A roentgenogram, taken August 6, 1936, showed irregular thickening of the apical pleura on the left side. The parenchyma of the lungs was clear. There was no roentgenological evidence of tuberculosis."

In June 1937 the patient had still another attack of left pneumothorax. During the previous year he had been well. Upon returning home from a long voyage he carried two suitcases up two flights of stairs and immediately developed pneumothorax, again on the left side. The roentgenogram revealed almost complete collapse of the left lung.[2]

[2] Additional information concerning this patient was given in a letter from Dr. Flynn, dated September 21, 1938: "When I wrote you last, in 1937, Mr. C. was having his third and most severe attack of spontaneous pneumothorax on his left side. He recovered from this nicely and then, in October 1937, when in

I have seen three more cases of this interesting condition which I shall describe briefly.

Case 5. A shoe salesman, twenty-nine years of age, entered the Johns Hopkins Hospital (History No. 67190) January 11, 1936, complaining of severe pain in the chest. At about 5.45 o'clock on the afternoon of January 11, while walking from work, he was seized suddenly with a severe, sharp, stabbing pain over the lower part of the left chest. Slowly he walked to a nearby restaurant, where he usually ate his dinner. While sitting at the table, waiting to be served, the pain became so severe that he nearly fainted. A neighbor led him from the restaurant into the open air where he soon revived. He hailed a taxi and was driven to the hospital. The bumping and jolting of the cab caused such excruciating pain that it was almost unbearable.

He was a well-nourished, muscular man, obviously in great pain. Over the left axillary area were found the physical signs of a partial pneumothorax. The area of cardiac dulness was much diminished in extent. Over the lower portion of the sternum and to the left of it, in the fourth and fifth interspaces, there were curious crunching, clicking sounds varying in intensity with each systole. A roentgenogram taken the following day revealed a partial pneumothorax on the left side but nothing else abnormal. The patient made a prompt recovery; the pain soon subsided, the curious sound over the heart disappeared, and the pneumothorax receded. Another roentgenogram of the chest taken January 30, demonstrated perfectly normal conditions.

Case 6. A sixteen year old white boy was admitted to the Johns Hopkins Hospital (History No. 100313) on March 11, 1937, complaining of pain on the right side of the chest. He had been in the hospital on two previous occasions, and at other times had been followed regularly in the Out-Patient Department. He had moderately severe

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California, he suffered his first attack on the right side which involved about forty per cent of the right upper. We saw him the first of November, following this California attack, and found the lung, almost, but not quite, completely expanded. A month or so after this he had another small collapse on this same right side and early in February 1938 he had his third attack on the right side making six attacks in all. Since then, as far as I know, he has been quite well."

diabetes which had been satisfactorily controlled by diet and insulin. The middle of February he had had grip and during convalescence went off to the country to visit an aunt. It is probable that during this visit vigilance had been relaxed as regards diet and the taking of insulin. On March 10, shortly after returning home, he complained of having no appetite, ate nothing all day, and therefore took no insulin. At about three o'clock the following morning the mother was awakened by hearing the boy cry out with pain. When she went to him he complained of severe pain over the right lower chest. At the end of five or ten minutes the pain was easier and he fell asleep. When he awoke at seven-thirty he again complained of severe pain in the right side and the mother noticed that he was breathing rapidly and deeply. A physician was called who heard fine crackling râles over the lower front of the right side of the chest and fearing the boy was developing pneumonia had him taken at once to the hospital.

On admission the temperature was 96°, the pulse 120, respirations 35; the blood pressure, systolic 90, diastolic 60; the leucocyte count 28,500. The boy was very drowsy, the face flushed, extremities cold and livid, respirations rapid and very deep, the eyeballs soft, the tongue and skin very dry. Over the lower front of the right side of the chest and at the base in back, the breath sounds were diminished in intensity and numerous fine, crackling, superficial râles were heard. The urine contained a large amount of sugar and abundant acetone.

By the use of appropriate measures the diabetic coma was promptly controlled. The following morning the boy was bright and alert, the pain had disappeared and he was comfortable and at ease. The evening before, subcutaneous emphysema had been noted above both clavicles. On this morning it was more pronounced and extended up the neck on both sides to the ears. Over the whole sternum, and louder still over the heart, numerous crackling, popping sounds could be heard greatly accentuated with each contraction of the heart. The roentgenogram demonstrated air in the mediastinum, in the tissues lying between the heart and the anterior chest wall, and in the subcutaneous tissues of the neck.

From then on the boy felt perfectly well. The crepitation in the neck soon disappeared, the crackling sounds over the heart subsided and at the end of eighteen days he left the hospital in good condition.

The temperature on admission was 96°; later in the day it rose to 101.4°; the following day it remained in the neighborhood of 100°; on the third day it fell to normal and thereafter varied between 98° and 99°. The leucocyte count on admission was 28,500; the following day it fell to 5,000; thereafter it varied between 5,000 and 6,000.

I am indebted to Dr. A. S. Schwartz, Resident Physician at Sinai Hospital, Baltimore, for the privilege of observing the following patient.

Case 7. Dr. L., 25 years of age, resident obstetrician at Sinai Hospital, is a short, stockily built man of vigorous appearance. He had always been robustly healthy, never seriously ill. On September 6, 1937, while eating lunch, he began to notice pain in the lower left axillary area. The pain gradually grew worse but it was not unendurable. He finished the meal, without speaking of the pain to his associates, and walked to his room to lie down. As he walked through the corridor the pain rapidly increased in severity and shifted over the heart, radiating to the left shoulder and to the left side of the neck. Upon reaching his room the pain had become so intense that it was only with great difficulty that he got to the telephone and called for aid. It was impossible for him to lie down, for when he attempted it the pain became unbearable. It was somewhat eased by sitting bolt upright upon the edge of the bed.

Dr. Schwartz was summoned and when he arrived found the patient suffering great pain. There was no cough, no cyanosis, no dyspnoea. Examination of the lungs was entirely negative. The heart was not enlarged, the sounds were somewhat distant but otherwise normal in quality except for a faint systolic murmur at the apex. The conspicuous thing was a noisy to and fro grating, synchronous with the heart beat, heard over the heart and as far to the left as the anterior axillary line. This sound was loudest when the patient lay down, it disappeared almost entirely when he sat erect.

I saw the patient twenty-four hours after the onset of pain. At the time of my visit he was lying propped up in bed with an ice bag over the heart. He was definitely apprehensive and lay very still because when he moved about the pain over the heart returned. The apex beat of the heart could be seen faintly in the 5th interspace inside the nipple line. The usual area of cardiac dulness was replaced by a

hyperresonant percussion note. As the patient lay upon his back the heart sounds were clear and of normal quality. The heart's action was slow and regular. When he shifted to the left side loud bubbling, crackling sounds occurred synchronously with the slow beating of the heart, louder with systole than with diastole. There was no subcutaneous emphysema in the neck. The pain soon subsided and after a few days the curious sound over the heart had disappeared. Thereafter the patient promptly recovered, in a short while he returned to work and since then has been perfectly well. The patient had no fever. The pulse and respiratory rates were not elevated. The blood pressure was within normal limits. The leucocyte count was 8,800. The sedimentation rate was normal. The roentgenogram gave no evidence of disease of the lungs. The heart was normal in size and position. There was no indication of air in the mediastinum. The electrocardiogram showed a prominent S-wave in the first lead with slight tendency to right axis deviation.

These clinical observations demonstrate clearly that the pulmonary alveoli of healthy persons may rupture and allow air to escape into the surrounding connective tissue when there has been no trauma to the chest, and no effort which might raise abnormally the intrapulmonary pressure. As you have heard described, the symptoms have come abruptly as the patient sat in a chair, stood, or moved quietly about. These circumstances justify the use of the term *spontaneous* even though it may be questioned whether normal alveolar walls can rupture so easily. When we consider the many daily occasions upon which the lungs, without harm, are greatly distended it is difficult to conceive of the alveolar walls rupturing when there is put upon them no unusual strain. It may be that for obscure reasons an alveolar wall here and there becomes attenuated and weakened but why and how this should occur we do not know. All we can say is that alveoli may rupture even when they show no gross evidence of disease.

After the escaped air has infiltrated the surrounding connective tissue it must travel along the fascial planes towards the mediastinum or towards the visceral pleura. In cats, whose lungs have been ruptured by forceful distension, Macklin has demonstrated that the air

travels towards the mediastinum along the sheaths of the arteries, and often there are continuous channels from the peripheral alveoli to the hilus. The interstitial tissue about the bronchi contains no air. The exact point of alveolar rupture cannot be demonstrated. In experimental animals the pressure gradients seem always to force the air from the periphery to the mediastinum, but it is possible that under special circumstances the air may travel to the visceral pleura producing a subpleural bulla. I shall refer again to this possibility in speaking of the frequent occurrence of pneumothorax in cases of mediastinal emphysema.

Air having reached the hilus, spreads out in the mediastinum, collecting in bubbles along the borders of the mediastinum and about the blood vessels, infiltrating the tissues that lie between the heart and the anterior chest wall. The distension of the mediastinal tissues causes pain, often of an extreme degree, which may radiate to the shoulder and down the left arm as does the pain of angina pectoris. There is also at times an alarming feeling of pressure or distension under the sternum; at other times pain on deep breathing, on swallowing, and with movements, such as turning the head, which pull upon or distort the mediastinal tissues.

The air may remain trapped in the mediastinum and gradually be absorbed or it may burrow along the fascial planes and appear at the jugulum and above the clavicles, spreading up the neck and over the front of the chest. It is quite possible that it may follow the aorta and esophagus, pierce the diaphragm, and infiltrate the retroperitoneal tissues. I found no evidence to indicate that the air had taken this course in the cases of spontaneous mediastinal emphysema I have reported, but it is well known that retroperitoneal emphysema often follows traumatic mediastinal emphysema and recently mediastinal emphysema has been observed after the injection of air into the perirenal tissues preparatory to roentgenography.

In two of the seven cases I have observed the interstitial and mediastinal emphysema was accompanied by pneumothorax. It is interesting to speculate upon the manner of occurrence of the pneumothorax. The combination of mediastinal emphysema and pneumothorax occurs often after trauma to the chest and regularly in animals when a high degree of mediastinal pressure is induced by overinflation

of the lungs. For instance in recording his experiments upon cats, Macklin describes the results as follows: "The picture of the animal during the experiment varies considerably, depending upon the air pressure used and the duration of insufflation. If the pressure is high a swelling of the abdomen and chest is quickly seen, with immediate cessation of respiratory movements. The swelling of the chest is often abrupt when the "break-through" from the mediastinum occurs. If the pressure is low the enlargement of the abdomen and chest comes on slowly and almost imperceptibly, and external evidence of injury may be afforded only by the stopping of breathing. If insufflation be continued sufficiently vigorously the root of the neck swells, and later the axillae, as air extends through the connective tissue out of the superior mediastinum along the course of the great vessels, and if the input be still continued the whole side of the animal swells by extension of air down from the axillae in the superficial fascia, and the body becomes tense."

When, after death, the chest is opened, air escapes, showing that it had been held under increased pressure, and both lungs are totally collapsed, the pleural cavities being filled with air. There can be no question that at least in most instances the air reaches the pleural cavities through a rent in the delicate wall of the mediastinum. In some cases Macklin was able clearly to demonstrate the point of rupture through the mediastinal wall. He sought carefully for a tear in the visceral pleura by immersing the lungs in water and compressing them but was never able to find one. By inducing pneumothorax in animals and raising the intrapleural pressure a bilateral pneumothorax is produced but never does air penetrate the mediastinum. By direct experiment it is very easy to force air from the mediastinum into the pleural cavity but it is never possible to force air from the pleural cavity into the mediastinum.

These experimental facts strongly suggest that the pneumothorax which often accompanies mediastinal emphysema is produced by escape of air from the mediastinum. It is possible that in some cases air may travel along the interstitial bands of the lung to the pleura and form a subpleural bleb which may rupture. However, it has never been demonstrated that this actually occurs and therefore it seems altogether likely that in most instances, if not in all, the air reaches

the pleural cavity through the mediastinum. These considerations may throw some light upon the obscure etiology of spontaneous pneumothorax. We have been accustomed to ascribe the escape of air to the rupture of emphysematous bullae and to minute pleural tears produced by the tug of adhesions. These explanations have never been altogether convincing and I think that we must now at least entertain the possibility that the initial lesion of spontaneous pneumothorax may be interstitial emphysema of the lung with escape of air to the pleura through the mediastinum.

Surgeons comment upon the fact that mediastinal emphysema after trauma to the chest is usually accompanied by pneumothorax and under these circumstances also we may assume that usually the pneumothorax is caused by air leaking through the mediastinal wall. The air in the pleural cavity often is under high pressure, and the difficulty with breathing, the cyanosis, and the circulatory collapse, which commonly result, are generally described as the effects of the tension pneumothorax. It may well be that these symptoms are the direct result of greatly increased pressure in the mediastinum. The effects of high mediastinal tension have been studied experimentally and they are precisely the same as those of increased intrapericardial pressure. When the pressure reaches the level of the venous and intraauricular pressure the veins and auricles collapse and the circulation of the blood is stilled. The threatening effects of increased mediastinal pressure have been relieved and life saved by a timely incision which furnishes an exit for the pent up air.

There is nothing new about the occurrence of interstitial emphysema of the lungs and mediastinal emphysema, for they have been observed for hundreds of years. Laennec gave the first accurate description of the pathological anatomy but long before his time physicians had recognized the occurrence of interstitial emphysema of the lung by noticing subcutaneous emphysema about the neck after trauma to the chest and after distension of the lungs by violent effort when the glottis is closed. It has been observed in new-born infants after attempts at resuscitation; in children after severe paroxysms of coughing or crying, in pneumonia and bronchial asthma; after straining at stool, during childbirth and after heavy lifting. Apparently, the diagnosis of mediastinal emphysema was made only when air appeared in the

subcutaneous tissues of the neck. This is surprising since the symptoms are distressing and the physical signs, when once understood, are clear in their implication. I must confess that I was utterly baffled by the clinical manifestations of the first case I encountered, but in the light of subsequent experience I am confident that now I should not have the slightest difficulty in appraising at once the true state of affairs. The character of the symptoms alone would immediately arouse my suspicion and the curious sound heard over the heart is altogether characteristic and distinctive.

As far as I can ascertain, heretofore the spontaneous occurrence of interstitial emphysema of the lung and mediastinal emphysema, has not been recognized. I can find no clear description of the condition in medical literature nor have I found one physician among the many to whom I have spoken about these interesting symptoms who has been familiar with them. In contrast to this, many have been convinced that the occurrence of spontaneous emphysema is the correct explanation for bizarre and puzzling clinical situations they had previously encountered and which at once recurred to their memory. This is remarkable since the condition seems to be not at all rare. In the short space of five years I have observed seven cases and more and more physicians report to me that they are now recognizing the condition.

The distinctive sign of mediastinal emphysema is the peculiar sound heard over the heart with each contraction, due, no doubt, to compression of the air-filled mediastinal tissues which lie between the heart and the anterior wall of the chest. It is a peculiar sound, different from any other sound heard over the heart. Nearly every observer uses different adjectives to describe it, for instance, crunching, bubbling, crepitant, crackling, clicking, popping, and yet when once heard the nature of the sound could never again be confused. There is evidence that this sound has been heard before but its significance has not been emphasized. Friederich Müller speaks of fine, bubbling, crepitations occurring synchronously with the beating of the heart as an early sign of mediastinal emphysema. Hoffmann repeats this observation. McGuire and Bean interpret the "pericardial knock" of Smith, and of Lister, as another description of the same sound.

In order to mark clearly the essential clinical features of spontaneous interstitial emphysema of the lungs and mediastinum I shall summarize the important symptoms.

1. Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

2. When the air reaches the mediastinum, distending the mediastinal tissues, the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum; sometimes it radiates to the back; at other times to the neck and shoulders, rarely to the arms. Accompanying the pain there is often a sensation of pressure or of expansion beneath the sternum.

3. There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leucocyte count are very little if any altered.

4. In many instances a peculiar and distinctive sound is heard over the heart synchronous with its contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

5. The area of cardiac dulness is diminished or completely obliterated, the dulness being replaced by a hyperresonant percussion note.

6. Pneumothorax often occurs. The pneumothorax is usually small and may not be suspected until a roentgenogram of the chest has been taken. Pneumothorax was discovered in two of the seven cases I have observed, in both instances on the left side. I see no reason, other than accidental, why it should have been on the left side and am inclined to predict that in other cases it will be found upon the right.

7. The roentgenogram is a valuable aid in establishing the diagnosis. In instances in which the characteristic sound over the heart is absent the roentgenographic evidence of air in the mediastinum may be decisive.

8. When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

I have been impressed by the helpful evidence furnished by the roentgenogram, and am indebted to Dr. John W. Pierson for his interest in this aspect of the condition. The most convincing picture is seen in the lateral roentgenogram when the tissues between the

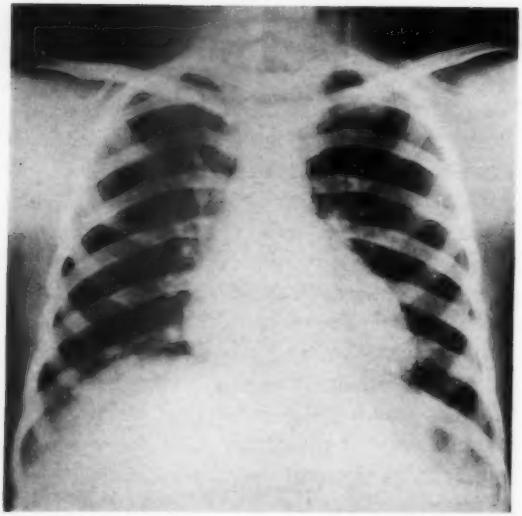

FIG. 1. X-RAY PICTURE OF CHEST. CASE 2

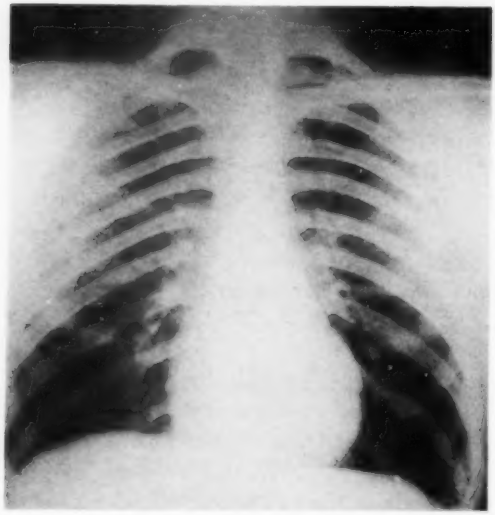

FIG. 2. X-RAY PICTURE OF CHEST. CASE 5

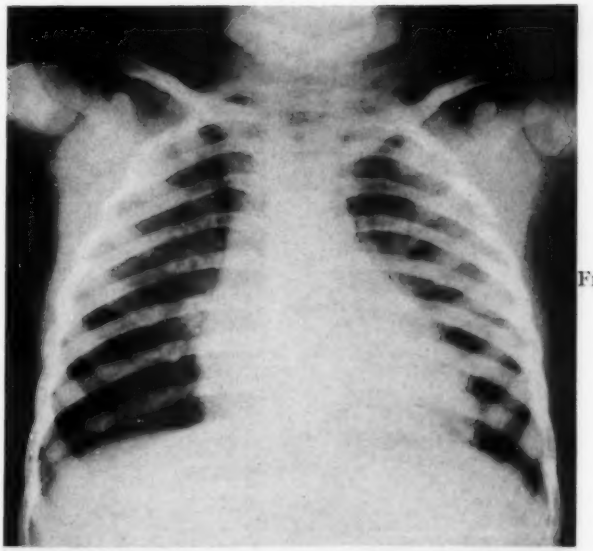

FIG. 3

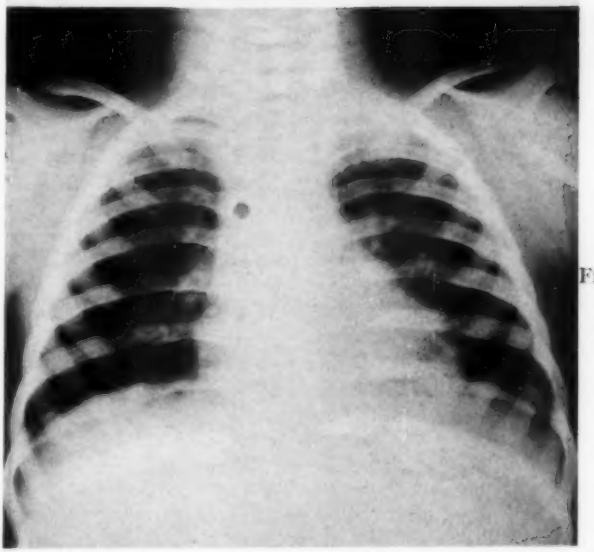

FIG. 4

FIGS. 3 AND 4. X-RAY PICTURES OF CHEST

In upper picture, note band paralleling left border of heart, and air in tissues of neck. Lower picture taken 3 days later, after absorption of air.

heart and anterior wall of the chest are infiltrated with air. However, such convincing proof cannot always be obtained and in its absence we must very carefully inspect the antero-posterior film for evidence of air in the mediastinum. The evidence consists of a sharp and distinct line running parallel to the border of the heart. This line we interpret to be the outer wall of the mediastinum. We have seen it in three cases, in all three running parallel to the upper portion of the left border of the heart as illustrated in figures 1 and 2, from Cases 2 and 5, respectively. The view, that this line really marks the border of the mediastinum, is strongly supported by figures 3 and 4 which reproduce the roentgenograms of a child three years of age who developed mediastinal emphysema during an attack of bronchopneumonia. The diagnosis was clearly established by the presence of air in the subcutaneous tissues of the neck and about the clavicles. In figure 3 a very distinct band is seen running parallel to the left border of the heart. In figure 4, taken three days later when the air had been absorbed, the line is no longer visible.

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GENERALIZED TORULA INFECTION

Case Report and Review with Observations on Pathogenesis

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Torula is a yeast-like organism belonging to the class *fungi imperfecti*, so called because no generally accepted description of a life cycle has been recorded. Todd and Herrmann (10) have recently described various forms found in cultures grown from a case of torula meningitis and have arranged these as stages in a complete life-cycle of the organisms. These observations as far as we know have not been confirmed.

The exact relationships of the organisms which we call yeasts and molds, have never been determined and none of the numerous classifications proposed has been universally adopted. Thus any discussion of the classification or identification is unsatisfactory. Except for the characteristic spore formation within the vegetative cell-body (ascospore), the various species of torula are quite like the true yeasts or saccharomycetes, and are excluded from the true yeasts only because of the lack of this characteristic reproduction. Torula is yeast-like in that it reproduces by budding, has the characteristic spheroid or oval form many times larger than bacteria, and possesses a well defined doubly-refractive wall. It is segregated from other members of this group in that reproduction occurs only through budding, no mycelia or spores are formed, and sugars are weakly fermented if at all. These characteristics apply to the pathogenic torulae. Numerous nonpathogenic forms have been described which ferment various sugars. *Cryptococcus* has recently come into rather general use as the name for the pathogenic organisms of this group.

A majority of the cases of torula infection in man have shown involvement of the central nervous system. Extraneural invasion

has been most frequent in the lungs. The occurrence of a widespread generalized infection with this yeast has been known since Verse's (3) report, in 1914, of a case in which he found lesions scattered throughout the organs of the body. Only four similar cases have been recorded since that time. In this report of the sixth case of generalized torulosis we have included a review of the preceding accounts together with a few observations upon the pathology of torula infections in man and in experimental animals.

The reports of torula infections in man have been complete in only a few of the cases. Frequently the diagnosis has been entirely unsuspected until microscopic examination of autopsy material, so that no cultural studies have been made either antemortem or postmortem to establish clearly the etiology of the lesions reported. Eleven cases have been reported without complete autopsies. In the present case the yeast was isolated from the spinal fluid almost two months before death and the clinical picture carefully considered. The cultural characteristics of the yeast and its animal pathogenicity were studied with cultures taken both before and after death.

CASE REPORT

T. J., a colored girl, aged 4 years, was admitted to Provident Hospital, June 22, 1936, with the complaint that "it hurts her to urinate and when she does, she has spasms."

Family history: Father, aged 73, has advanced arteriosclerosis. Mother, aged 39, is well but her "mind is not sound." Sister, 3 years old, and brother, 10 months old, are living and well. There is no history of syphilis, tuberculosis, diabetes, allergic or other familial diseases.

Past history: The patient was born spontaneously after a normal pregnancy and weighed seven pounds. Her neonatal condition was good and she was breast fed for eighteen months. Since then she has been on a diet sufficient in quantity but probably lacking in proteins and vitamins, especially vitamin D. Her development was average. She was walking and saying words before 1 year of age. Her teething was normal. She had no illnesses before the present one and had no infectious diseases or immunization against them. No operations, fractures or severe accidents.

Social history: She has lived in the country all her life in a shack of the poorest tenant-farmer type. Her father makes barely enough to keep his family together by working his patch of ground and by doing odd jobs. The mother, a definitely feeble-minded negress adds little to the care of either house or children.

Present illness: Three months before coming to the hospital the child began

having attacks of fever, and scanty, painful urination. Several weeks later, about two months prior to admission, she developed generalized convulsions which occurred frequently, lasted ten to fifteen minutes and were followed by periods of deep sleep. About this same time her vision began to fail so that she could not recognize members of the family for the week preceding hospitalization. By this time she lay in one position in bed almost constantly, ate little and was markedly constipated. Several times daily she cried out because of what seemed to be severe abdominal pain. Her stupor increased, the convulsions continued and she was brought to the ward.

Physical examination: Weight 14 kgs. Height 102 cm. Head 51 cms. Chest 47 cms. Abdomen 40 cms. Temperature 99°F. Pulse 110. Respirations 14 to 25. *General appearance:* The patient is a poorly developed, emaciated colored girl of 4, lying on her side with her knees drawn up and her head retracted. She is quiet when not disturbed, and in no apparent pain. She makes no response to loud noises and will not speak. *Skin:* The skin is normal in temperature, rather dry. There is a faint mottling on the trunk, particularly the abdomen, as if there had been measles present some weeks before. Slight cyanosis of fingers and toes is present. No abrasions or other lesions. *Glands:* No general glandular enlargement, but small shotty nodes can be palpated in both axillae, the groins and the posterior cervical triangles. *Head:* Tender to pressure all over. Cracked-pot sound on percussion. No unusual masses or depressions. Hair is normal. *Eyes:* No extra-ocular paralysis, occasional right internal strabismus. Pupils react slowly to light. *Fundi:* (Dr. Frank Walsh) "R. E. Media clear. No papilloedema but diffuse oedema most marked at macula. L. E. Same as right. Nerve heads are of normal color." *Ears:* Totally deaf, at least no response is made to loud noises. No discharge. Left drum normal. Right drum has a clean perforation. Canal walls normal. *Mouth:* Breath foul. Tongue heavily coated. Teeth normal in number; dirty; enamel thin; several small cavities. Buccal surfaces are clear. The pharynx is mildly injected and the tonsils small and smooth. When she cries her voice is normal. *Neck:* Stiff and retracted. There are no unusual masses. Trachea is in midline. Thyroid palpable but not enlarged or unusual in consistency. *Chest:* There is evidence of old rickets in the enlarged costochondral junctions and Harrison's groove; otherwise the contour is normal. Respiratory movements slow and grossly irregular but equal on the two sides. Lung bases descend normally. *Lungs:* Clear to percussion and auscultation. *Heart:* Is not enlarged to percussion; the rate is 110; the rhythm regular and the sounds normal. A faint systolic murmur is present along the left sternal border. The pulses are equal. *Abdomen:* The soft scaphoid abdomen is not tender to palpation. The spleen can be felt at the costal margin, and the liver one finger's breadth below. *Genitalia:* The external genitals are not inflamed and are normal in contour. There is no vaginal discharge. *Rectum:* Examination negative. Anus is normal. *Extremities:* Normal. *Neurological:* The child is too weak to walk or stand but she can feed herself and no ataxia is evident. There is slight hypertonia of all the muscles.

Sensation to pain and touch is present. In fact, there seems to be hyperesthesia most of the time. The knee jerks cannot be obtained and other reflexes are sluggish. She is blind and deaf, has a slight weakness of the right VI and VII nerves; otherwise the cranial nerves are normal.

Laboratory findings: Intracutaneous tuberculin test negative to 1 mg. Blood Wassermann negative. *Blood:* R.B.C. 4,200,000; Hemoglobin 79% (Sahli); W.B.C. 8,900, PMN 78%, Lymphocytes 10%, Monocytes 12%. Platelets appear normal. No parasites. *Spinal fluid:* Came out under increased pressure, was definitely cloudy and light gray in color. An unusual feature was that most of the sediment fell to the bottom of the tube within a very few minutes, much more quickly than the cells of a purulent meningitis settle out. There was much globulin present in all the specimens. The cells varied from 100 to 400 per cubic mm. and were mostly polymorphonuclear leucocytes although many lymphocytes, about 25%, were always present. No bacteria were seen in the smear but, in both the counting chamber and the stained preparation, there were innumerable, heavy walled, highly refractile, acidophilic, globoid bodies, usually oval in shape and varying from 3 to 15 micra in length and from 2 to 12 micra in breadth. Occasionally a budding form could be seen. No bacteria grew from numerous cultures but these same yeastlike bodies could be recovered freely from blood agar plates and Sabouraud's medium. Four mice were inoculated with spinal fluid, two intraperitoneally and two intracerebrally. They all died between the seventh and tenth day after inoculation. In all of them small nodular lesions were scattered throughout the various organs. The brain, lungs and liver were affected most conspicuously. Many of the areas were jellylike. From all of them could be recovered the same double-walled yeastlike bodies identical with those found in the spinal fluid of the patient. No histological studies were made. The spinal fluid Wassermann was negative. The sugar was 35 mg%. The colloidal gold curve was 1122100000. *Blood culture:* Negative. *Urine culture:* Staphylococcus albus. *Urinalysis:* Specific gravity 1.020. Acid. Straw color. Albumin—trace. Sugar negative. Acetone negative. Diacetic acid negative. Bile negative. No W.B.C., R.B.C. or casts. *Stool:* Contained no mucus, blood, parasites or ova. Normal in color, odor and consistency.

Course: The child's course in the hospital, from the time of her admission on June 22, 1936 to her sudden removal against advice on July 14, 1936, was one of slow but progressive loss of strength. She had several generalized convulsions during the first few days of her stay but during the last week was in a stupor the greater part of the time. She responded to painful stimuli with shrill incoherent outcries, only to lapse back into a stertorous stupor. Feeding became more difficult and constipation severe. At one time she developed signs of intestinal obstruction but these soon disappeared without surgical intervention. None of the dysuria mentioned in the history was observed in the hospital. It is interesting that at no time while she was under observation did her temperature rise above 100.2 degrees F. except on two days when she became dehydrated after vomiting. Most of the time the temperature was normal.

After leaving the hospital she was taken home and remained in much the same state until her death two months later.

Autopsy report

The *body* is that of a poorly nourished 4 year old colored female. There is only slight rigor mortis although the body has remained at room temperature approximately 16 hours since death. Other than a slight purplish-red color of the lips and a small scar below the umbilicus, the *skin* and *mucous membranes* show no abnormalities. The *cranium* is noticeably enlarged and both the anterior and the posterior fontanelles are soft. The *serous cavities* are not remarkable. The *heart* is normal. There is moderate injection of the *tracheal* and *bronchial mucosa*. The *lungs* are crepitant but somewhat firmer than normal. The cut surfaces of the upper and lower lobes are reddish-gray with numerous scattered gray areas two to three mm. in diameter. The Malpighian bodies of the slightly enlarged *spleen* are numerous but not conspicuous. The surrounding pulp is firm and light red in color. The *stomach*, *intestines*, *pancreas*, *liver*, *adrenals*, *kidneys*, *uterus*, *Fallopian tubes*, and *ovaries* show no lesions. There is slight reddening of the *bladder mucosa* about the trigone. Similar hyperemic areas are seen in the mucosa of the *vagina*. The peribronchial, cervical, inguinal, axillary and retroperitoneal *lymph nodes* are normal. The intima of the very elastic *aorta* is quite smooth. The *dura* is very tightly adherent to the skull along the suture lines and at the fontanelles. The somewhat enlarged *brain* presents an extraordinary picture. There is a peculiar, widespread meningitis. In the meninges about the base of the brain there is a large quantity of thick, tenacious, mucoid material surrounding the brain stem and filling the crevices between the sulci. A layer of this same mucoid material completely covers the surface of the cerebral cortex. On the under surface of the frontal lobes the brain tissue is riddled with small areas of a similar mucoid material giving the brain a mottled appearance. When the superior longitudinal sinus is opened numerous small purplish nodules are found projecting into the venous channel. These are larger and rounder than the Pacchionian granulations. At one point attached to the lining of the sinus and projecting into the lumen, there is a flattened mass, 1.5 cm. in length, 3 mm. in greatest thickness. Gross sections of the brain show remarkable alterations. There are large areas, particularly in the region of the basal nuclei (Fig. 1), where practically the whole brain substance has been replaced by soft, translucent, mucoid masses. The fornix is similarly altered. In the left temporal lobe there is another large oval area, approximately 5 cm. by 3 cm., which has undergone this mucinous change. Throughout the entire brain there are small areas filled with this jelly-like material. These small cysts are most numerous in the gray matter of the convolutions and in certain areas are almost confluent. The white matter is relatively free from cysts. Quite the same change is found in the cerebellum where the folia are separated by mucoid material (Fig. 2). The cerebro-spinal fluid is cloudy. There are no gross lesions in the hypophysis. Several soft areas, 5 or 6 mm. in diameter, in the bones of the

middle fossa of the skull are filled with a yellow gelatinous material similar to that in the meninges. These soft areas extend into the bones but not through them.

Although the body remained without refrigeration for an interval of some sixteen hours from the time of death until autopsy we do not believe the widespread neural and meningeal growths are the result of any extensive postmortem invasion. As stated above in the history of this case the child had generalized convulsions four and one-half months before death, and for two months prior to autopsy had been in a stuporous state responding only to painful stimuli. Ventriculograms taken two months before death demonstrated marked alteration of the ventricles, with thinning of the bones of the cranial vault. All of these facts might indicate long standing, widespread involvement of the brain and meninges. Other cases of comparable central nervous system invasion have been described (8) in which autopsies were performed upon refrigerated bodies. Lesions elsewhere in the body, having a more marked cellular reaction, give no evidence of postmortem growth. The parenchyma of such organs as the kidneys, liver, and pancreas is as well preserved as in the majority of cases which are routinely refrigerated until the time of autopsy. In the animals used in later experiments no marked postmortem growth was found to occur, even when the bodies were left at room temperature and were not autopsied until approximately twelve hours after death.

Microscopic pathology

Brain from the region of the inferior olive: This section includes a portion of the ventral surface of the brain-stem in the region of the olive and a small area of the laterally lying cerebellum. The yeast cells which are clearly seen in this section are for the most part round or slightly ovoid bodies varying greatly in size, from 2 to 25 micra in diameter. With the hematoxylin-eosin stain their cytoplasm is generally colorless and it may be either clear, containing only one eccentrically placed refractile body, or coarsely granular, the granules being most numerous about the periphery of the cell. The cytoplasm is enclosed in a doubly refractive cell membrane, 1 to 2 micra in thickness, which is similar in structure to the cell wall of true yeast. This in turn is surrounded by a capsule 2 to 5 micra in thickness which is not stained by either hematoxylin or eosin, but is clearly demonstrated by using Wayson's stain. Sections stained by the latter method show many yeast cells with capsules as much as 10 micra in thickness. The width and prominence of the capsule varies, but they are not directly related to the size of the cell body. Between the capsules of the organisms both in the cysts and in the meninges, the spaces which appear clear and colorless in hematoxylin-eosin sections, contain a substance which can be stained blue with polychrome-methylene blue. This substance apparently is produced by the organism and is found also between the yeast cells in smears made from cultures grown on Sabouraud's medium. The shape of the fungi found within the substance of the brain is frequently distorted. Few of the budding forms are seen. It is impos-

sible to identify the normal meninges of the brain. The mucinous exudate surrounding the brain which was described in the gross examination, is seen in this section as a layer of material varying from 0.5 to 3 mm. in thickness which is composed almost entirely of a mass of torula cells imbedded in an amorphous matrix such as was described above. There is a moderate number of round cells diffusely scattered throughout the meningeal exudate. About certain of the meningeal vessels there is a perivascular round cell infiltration. No polymorphonuclear cells are seen. The meningeal infection extends into the substance of the brain via the perivascular spaces of the numerous small blood vessels. There are also two areas in this section where the process has extended directly into the nervous tissue without relation to the blood vessels. In the neural lesions torulae may be found either imbedded in oedematous brain substance containing a moderate number of round cells or, as is frequently seen, surrounded by normal nervous tissue showing no evidence of cellular reaction. Many fungi are seen lying in the immediate vicinity of intact nerve cells. A few small collections of yeasts are found in the brain tissue, apparently unrelated to the blood vessels. The brain tissue not directly involved in this process appears normal. The spaces between the folia of the cerebellum are filled with large numbers of torulae and their surrounding matrix. The substance of the cerebellum is heavily infiltrated with masses of the yeast cells. In many places this appears to be a direct extension of the process from outside the brain. The region of the Purkinje cells is a favorite site for the development of the cystic areas, although all parts of the cerebellum are affected to some extent. The distribution about the blood vessels is very striking in the cerebellum, particularly in the region of the dentate nucleus. Other sections from various portions of the brain show similar widespread alterations, the yeast infiltration being most pronounced in the gray matter.

Superior longitudinal sinus: Nodular masses, which are apparently extensions into the sinus along blood vessels and pacchionian granulations from the process in the meninges, invaginate the lining of the sinus and narrow it. These masses are composed of yeast cells either with or without loosely arranged mononuclear and epithelioid cells. The cellular reaction in this region is the greatest seen inside the skull.

Lung: There is widespread lobular pneumonia. Just beneath the pleura there is a large nodule which contains several large multinuclear giant cells and numerous torulae, and which shows marked round cell infiltration at its periphery. Other similar but smaller nodules or tubercles are scattered throughout the substance of the lung, generally lying close to some moderately large blood vessel. There are many fungus cells lying free in the alveoli throughout the lungs.

Spleen: Within many of the Malpighian bodies there are small clusters of torulae which are not surrounded by epithelial cells or engulfed by giant cells. Rarely these clumps of yeast bodies are found within the splenic pulp.

Kidney: The kidney substance in general looks quite normal except for a few widely scattered lesions about the invading yeast forms. These lesions are com-

posed of numerous yeast cells imbedded in masses of necrotic, structureless material, with moderate round cell infiltration at the periphery. The tubules surrounding these lesions are compressed and pushed aside. These areas bear no relation to the glomeruli.

Liver: In the periportal spaces there are numerous small tubercles composed of centrally placed torulae surrounded by round cells and epithelial cells.

Pancreas: Several small clusters of free torulae are surrounded by a narrow zone of necrotic pancreatic cells. There is no leukocytic reaction about these lesions.

Adrenals: There is no evidence in these organs of yeast infection.

Heart and aorta: The myocardium is normal. The wall of the attached aorta is normal except for a small area in the outer portion of the media which is infiltrated by a number of yeast cells. Here the elastic fibers are spread apart and broken although the cellular response is negligible.

Thyroid: Tubercles are found in this organ, containing only a few yeast cells but showing a very marked epithelial and lymphocytic response.

The other organs are not abnormal.

Mycology

A smear taken from the meninges at the time of autopsy and stained with methylene blue shows large yeast-like forms with buds. Gram stains of similar smears indicate that these yeast cells are gram positive.

Pure cultures of torula were grown on the original Sabouraud slants inoculated with material from the meninges over the base of the brain, the middle fossa, and the vertex.

In young cultures the small colonies were round, smooth and cream-colored. As growth progressed the colonies coalesced and spread out evenly over the surface of the medium. After six or seven days the cultures became somewhat darker, and after two weeks were dark brown in color, with a dry looking surface.

The yeasts from the colonies vary greatly in size. Many of the smaller torulae are only 1 or 2 micra in diameter while some of the larger forms are 10 to 15 micra. When studied in NaOH solutions and fresh ink preparations, the typical round, double-contour torulae are seen.

Stoddard and Cutler (2) described a "fur-like" appearance of certain of the torula cells seen in the lesions in experimental animals. Recently Dickson (11) has discussed a similar arrangement of fine radiating spicules on the capsules of coccidioides spherules. He concludes that these small prickles may be the result of growth in an unfavorable environment, due either to insufficient oxygenation or to the toxins which cause accumulations of pus in coccidioidal lesions. With Wayson's stain Dr. W. G. MacCallum has demonstrated the presence of the "fur" about certain of the yeast cells in the lesions of the brain and meninges in the present case. (Fig. 4.)

The following sugars were inoculated: dextrose, lactose, xylose, sucrose and

maltose. Gas was not formed in any of the sugars after three weeks. Acid was formed in dextrose and sucrose by the fourth day.

Cultures were grown on carrot media in an attempt to induce mycelium formation. No mycelia were seen in any of a number of NaOH preparations nor in stained smears made at intervals during a period of three weeks.

Rabbits, guinea-pigs, rats, and mice were inoculated subcutaneously and intraperitoneally with a heavy saline suspension of a 36-hour culture. The yeast was pathogenic for mice and rats. Pure cultures of torula were isolated from the organs of the mice and reinjected into a second series of these rodents. The second group likewise succumbed to the infection and the typical torula lesions, both macroscopic and microscopic, were found at autopsy.

In summary, we have isolated pure growths of the torula in original cultures taken at autopsy. The identify of the yeast has been established by (1) lack of gas formation in any of the five sugars inoculated, (2) weak acid formation in two of the five sugars inoculated, (3) characteristic morphology, (4) reproduction only by budding, (5) lack of mycelium and spore formation, (6) characteristic pathological changes in experimental animals the etiology of which was checked by isolation of pure cultures of the yeast from these lesions and reinjection into a second series of animals with the production of an identical infection.

DISCUSSION

(*A*) *Clinical picture of torula infection*

In reviewing the history and course of this case in the light of the pathological changes several things are noteworthy. It is remarkable that a disease caused by an infectious agent could give rise to such extensive tissue damage in many parts of the body, and still not be accompanied by fever. During the entire time that this child was under observation in the hospital her temperature remained practically normal. Another interesting feature of her case was the similarity of the course and physical findings to those of the cerebral degenerative disease *encephalitis periaxialis diffusa*, particularly the convulsions at the onset and the early loss of sight and hearing. Although the nodular lesions due to torula were scattered throughout the body, there was no symptom or physical sign to call attention to any of them except those in the lungs. All during the child's illness there was an occasional cough, and the x-ray picture of her chest, taken two months before death, showed increased hilar markings. However, there was nothing specific either in physical examination or in the x-ray picture to distinguish the pulmonary changes from those of any other low grade chronic lung infection. The

dysuria complained of at the onset of the illness had disappeared by the time the child was admitted to the hospital and no local basis was found for it in either laboratory or postmortem examination.

A point of interest in the examination of the spinal fluid and one which may be an aid to the diagnosis of torula meningitis, was the rapid settling out of the sediment when it contained many of the yeast bodies. As the fluid ran into the tube from the lumbar puncture needle it appeared gray and cloudy, but instead of remaining so for some hours, most of the solid matter settled to the bottom within ten minutes, giving the tube the appearance of having been centrifuged.

Many clinical reports of torula infection have been published and there are a good many pathological studies of the effect of this organism on the central nervous system. These have been reviewed in Freeman's (1) excellent article. However, the records of only a few patients which have been studied adequately have been published. It would be unwise to attempt to construct the clinical picture of so protean a disease from so few instances; the discussion will therefore be limited to the symptoms more commonly encountered when this organism invades the body.

The affinity of *torula histolytica* for the central nervous system is well known and various neurological manifestations most frequently call attention to the infection. On the one hand, the onset may be sudden with severe headaches, convulsions, and signs of increased intracranial pressure; on the other hand there may be a gradual loss of cerebral function and the use of the special senses, such as occurred in our patient. In either case headache is the most common and sometimes the only symptom. It may be accompanied by dizziness or faintness, often by signs of meningeal irritation, such as stiffness of the neck or back. When one considers the extent and variety of the intracranial lesions, it is not surprising that the clinical neurological manifestations are correspondingly variable. The disease may simulate acute or chronic meningitis, degeneration of the central nervous system, or brain tumor.

In the list of symptoms occurring in patients with generalized torulosis, cough is the most prominent after those mentioned above. The x-ray picture of the lungs shows little more than increased hilar markings or an area of chronic consolidation. The lung signs simu-

late those of slowly progressive pulmonary tuberculosis. The finding of yeast-like bodies in the sputum, while suggestive of torulosis, cannot be considered diagnostic until their pathogenicity has been proven. Several of the reported cases of generalized torulosis were complicated by tuberculosis, one by Hodgkin's disease and another by carcinoma. It seems that chronic illnesses of various kinds tend to make one more susceptible to infection by the fungus.

Although torula has been found in most parts of the body, it is unusual to have symptoms caused by its growth call attention to internal organs, except the central nervous system and lungs. Involvement of the skin occurs rarely although torula should be thought of whenever there is an undiagnosed indolent granulomatous lesion. Such slowly growing ulcerations have been described in the mouth and in the skin of various parts of the body. The initial lesion may be a pustule, and acneiform and nodular skin lesions have been seen. Torula and similar yeasts are common in our environment and often can be found on normal skin. However, the pathogenicity of the more prevalent forms has not been proven. Fungi may be present saprophytically in chronic ulcerative lesions caused by other infectious organisms. Often it is difficult to determine the rôle these fungi play in producing the pathological changes. When they go on to invade the glands, as they may, the infection is well on its way to becoming generalized, and once it does, the prognosis becomes practically hopeless.

In summary, then, the symptoms of torulosis are most apt to be those of infection or degeneration of the central nervous system. There may be chronic bronchitis, or peribronchial infections, or superficial lesions, usually granulomatous, occurring on the skin or mucous membranes. The lymph glands may be enlarged and nodular areas of infection may be found in any part of the body when the generalized disease exists.

Therapy is most unsatisfactory, and nothing has been of help in treating the generalized infection or the involvement of the central nervous system. Local skin or mucous membrane lesions sometimes may be treated successfully with iodides, or, in selected cases, by excision which would seem to be a wise procedure in view of the severity of the generalized infection.

(*B*) *Etiology and pathology of torula infection*

Freeman (1) has concluded from an extensive review of the literature on the subject of torula infection and from a study of material from 19 of the 43 cases reported up to 1931, that the types of organisms involved may be tentatively subdivided into three species according to the characteristics of the torula and the nature of the neural lesion produced.

In one type (Type I) the organism is characterized by its large size, occasional umbrella shape, narrow capsule, and feeble invasive power for the brain, with relatively greater reaction provoked in the mesodermal elements. Another type of organism (Type III) shows a very active tendency toward cyst formation in the brain, induces little reaction, is of small size, has a large capsule, and may be easily cultivated. An intermediate variety (Type II) may lie midway between these.

A study of the morphological and cultural characteristics of the yeasts, and of the pathological lesions both in experimental animals and in the five autopsied cases in our files, has brought forth certain fundamental discrepancies in such a classification. That different strains of torula possess characteristics not common to the entire group is undoubtedly true. This contention is supported by the variations in pathogenicity, in pigment production, in sugar fermentations, and in cultural requirements. However, the appropriateness of the criteria of subdivision advocated in the foregoing classification is debatable. The size and shape of the organisms, particularly as judged from the yeasts seen in sections of lesions, are unreliable factors in classification. Studies of test-tube cultures indicate certain fallacies in this regard. In any ordinary culture there are tremendous varations in size, the yeast cells frequently varying from 1 or 2 micra in diameter up to 10 or 15 micra, in the same smear. Two cultures of the same strain, one grown in a favorable, and the other in an unfavorable environment, may display a much greater variation in morphology than two different strains of torula grown under the same conditions. The predominant form of the torulae found in smears from the luxuriant growth of fresh Sabouraud slants, is a very small organism with numerous budding forms not unlike the organisms described in Type III cases. Smears of this same strain cultured on

carrot media show a predominance of a form more closely related to the yeast described for Type I, a larger organism with fewer budding forms and a narrow capsule. This lack of characteristic morphology has long been known as an important factor in retarding the purely mycological classification of these yeasts.

Noting the change in the morphology of the torula in the test-tube we wished to know if any characteristic species morphology was maintained when the yeast was injected into various experimental animals. Portions of a heavy saline suspension of a 36-hour Sabouraud culture were injected intraperitoneally and subcutaneously into mice, rats and guinea pigs. In microscopic sections the torula found in the lesions varied as greatly as the two extreme species in the aforementioned classification. In the mouse the organisms were predominantly small, with large capsules (Type III); while those of the same strain found in the corresponding tissues of the rat were generally larger, with narrower capsules and with rather indefinite outlines. The yeast cells in the lymph nodes of the guinea pig, the only structures involved, were of the larger variety.

The great inadequacy of morphology as an important characteristic of the infecting yeast is emphasized when we examine the human lesions. We have studied the tissue sections from the five cases of torula infection which we have in our files. In a single lesion a predominant type of torula may be found, but if we attempt to go further and establish a characteristic morphology for an entire organ such as the brain, or for the entire body in the generalized cases, we immediately encounter difficulty. The predominant form of torula varies from tissue to tissue, and in none of the five cases studied were we able to identify all of the lesions as belonging to a particular case by examining only the morphology of the yeast. In the present case, for example, the large cystic areas in the brain, with a minimal cellular reaction about them, are filled, for the most part, with the smaller organisms. In the same case the lesions which project into the superior longitudinal sinus, and those in the thyroid and kidneys, about which there is a more marked cellular reaction, contain organisms which are constantly larger, with rather faint outlines and very narrow capsules. Even in the same organ, the brain, wide variations in size and shape are found from field to field as seen in figures 5 and 6.

The labile nature of the yeast's morphology in the test tube, in experimental animals, and in actual human lesions greatly detracts from the value of this characteristic as an important criterion in species differentiation.

Classification of torula infections upon the basis of the pathological picture in autopsy material such as is presented in Freeman's scheme is also open to question. A careful study of the types of lesions that have been reported, particularly in the brain and the meninges, reveals cases showing all degrees of cellular reaction. The case reported in this paper is a good example of one extreme: widespread growth of the organism, accompanied by a minimal reaction. From this condition, cases illustrating all stages of reaction can be found up to the most advanced states, such as the lesions in the cases of Kindell (4), Chiara (6), Bettin (1), and Stoddard and Cutler (2) where there is a marked response of round cells and giant cells as well as areas which have become hyalinized, fibrotic and, in certain cases, caseous. Thus, with the gradual shading of one type of reaction into the next, it is difficult to make any sharp separation of the cases into three distinct classes.

Does the nature of the pathological lesion depend entirely upon the species of the infecting torula? The experimental lesions produced in animals suggest, although they do not necessarily prove, that there are other important factors to be considered. One cc. of a 36-hour culture of torula injected intraperitoneally into mice, caused death in 5 to 8 days. All of the organs were riddled with various sized torula cysts conforming in every particular to the character of human lesions associated with the so called Type III organism. There was essentially no cellular reaction and apparently very little resistance to the growth of the torula. White rats injected intraperitoneally with 2 cc. of the same culture died or were killed five to eight weeks later. In this apparently more resistant animal an entirely different type of lesion was found. The cellular reaction was quite marked. Typical tubercles were formed, composed of giant cells, epithelioid cells and lymphocytes. The centers of some of these lesions were necrotic and, in places, had become hyalinized. The pathological picture is similar to that which we find in human cases included under Type I. In brief, by injecting the same strain of

torula into a susceptible animal which is overcome in 5 to 8 days, and into a more resistant animal which withstands the infection for 5 to 8 weeks, the two extreme types of lesions have been produced.

The observations discussed above lead us to believe that the character of the pathological lesions, and the morphology of the organisms contained therein are both of doubtful significance in classification, and that any subdivision of the infecting agents based upon such criteria can be of little value either clinically or pathologically. On the other hand we believe that within a particular species there may be a significant correlation between the morphology of the organism and the type of the lesion. The smaller organisms are found in rapidly growing cultures situated in favorable environments in the test tube, and in human and animal lesions in which the cellular reaction and tubercle formation are inconspicuous, while the larger forms predominate in unfavorable environments in cultural media, and in human and animal lesions in which prominent tubercle formation indicates a greater defense reaction.

Our observations indicate that there is a variation in the degree of resistance offered to the growth of the fungus from tissue to tissue even in different parts of a single organ, as well as a variation of general resistance in different individuals. This variation in the human lesions has been noted by other authors. Crone, DeGroat, and Wahlin (13) remark, "The degree and character of the inflammatory response that the torula excites seems to vary greatly in different human cases. It may be feeble or absent, proliferative, or occasionally exudative, and its character cannot be entirely explained by the age of the lesion. In our experimental animals the inflammatory response seemed to be almost entirely histiocytic and its degree related to the local supply of cells capable of being mobilized as macrophages. Few in the brain, such cells were more numerous in the lung and peritoneum. The same general statement, applied to our human material, would be an exaggeration, although not an excessive one."

It is undoubtedly true that individual strains of torula differ in pathogenicity in a manner somewhat similar to the variations of virulence in other organisms. Instead of considering the importance of any species difference as the sole, or as the most important factor,

we believe the lesions of this infection are more readily explained as the result of the interrelation of factors such as the virulence of the strain, the resistance of the host and the hypersensitivity of the host, a phenomenon which has been demonstrated by Uerbach and Zach (9), reacting in the same manner as Rich (12) has described in the development of tuberculous lesions.

The Production of Cysts in the Brain: The mechanism whereby the cystic areas are formed in the brain is a question which has aroused considerable discussion in recent years. Stoddard and Cutler (2) originally named the yeast *Torula histolytica* because they believed that these cells possessed a certain lytic power which digested the nervous tissue and produced the material of unknown nature which filled these areas. Recently this digestive power has been denied by certain writers who contend that *Torula histolytica* is a misnomer and that the cysts are produced entirely by mechanical effects as the torulae increase in size and number. We believe that little information concerning this issue is to be gained by the study of the gross or microscopic lesions alone. After examining the central nervous system lesions in five autopsied cases, and sections from the brains of a number of experimental animals which show the cystic areas in all stages of development, no definite conclusion could be reached. The lesions might be interpreted as a result of either process or as a combination of both.

SUMMARY

(1) A case of generalized torula infection is reported in which there was involvement of the brain, meninges, lung, liver, spleen, kidneys, pancreas, thyroid, and aorta.

(2) In generalized torula infection the central nervous system is most likely to be involved, the lungs occasionally. Other organs seldom are affected to such an extent as to produce clinical symptoms.

(3) In general it may be stated that the smaller torula cells with wide capsules predominate in favorable environments in the test tube, in experimental animals, and in human lesions, while the larger forms with narrow capsules are seen more frequently in the presence of an unfavorable environment.

(4) The wide variations in resistance to this infection, from organ to organ in the same individual, and even within the same organ, make the classification of torula infections, based upon the character of the pathological lesion and the morphology of the invading torulae, of doubtful value.

(5) The character of the lesions caused by torula, is probably the result of the interrelation of factors such as the virulence of the strain of torula, the resistance of the host, and the hypersensitivity of the host, reacting in the same manner as has been described in the development of tuberculous lesions.

It was due to the efforts of Dr. Thomas L. Higdon of Wayside, Maryland and Dr. M. E. Wegman, Consulting Pediatrician of the State Health Department, that we were able to obtain an autopsy. We also wish to express our appreciation to Dr. F. B. Kindell of the pathology department of the Baltimore City Hospitals and Dr. A. R. Rich of the pathology department of the Johns Hopkins Hospital for their many helpful suggestions and criticisms in the preparation of this paper. We are indebted to Mr. Milton Kougl for the excellent photographs which he has prepared.

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PLATES

PLATE 1

FIG. 1. Transverse section through brain showing extensive involvement of gray matter and basal nuclei.

FIG. 2. Section from the cerebellum with spaces between the folia filled with gelatinous material produced by the torulae.

FIG. 3. Section from folia of cerebellum. Growth of torulae in the meninges and a typical small torula cyst in the brain substance are shown. (Hematoxylin-eosin stain. × 100.)

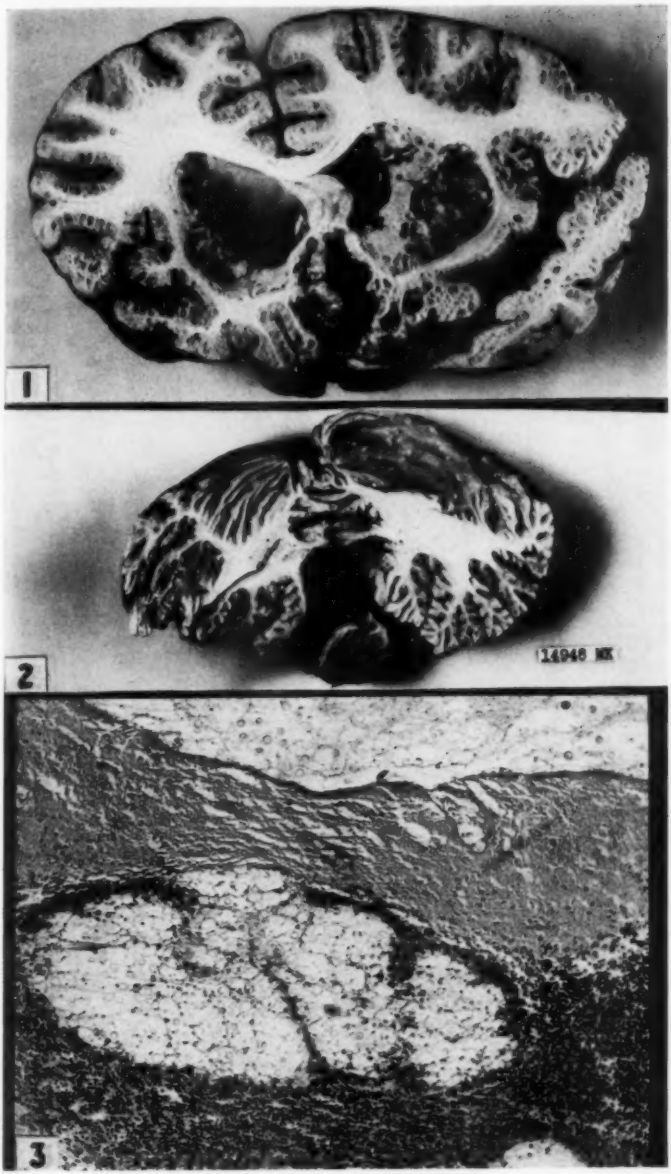
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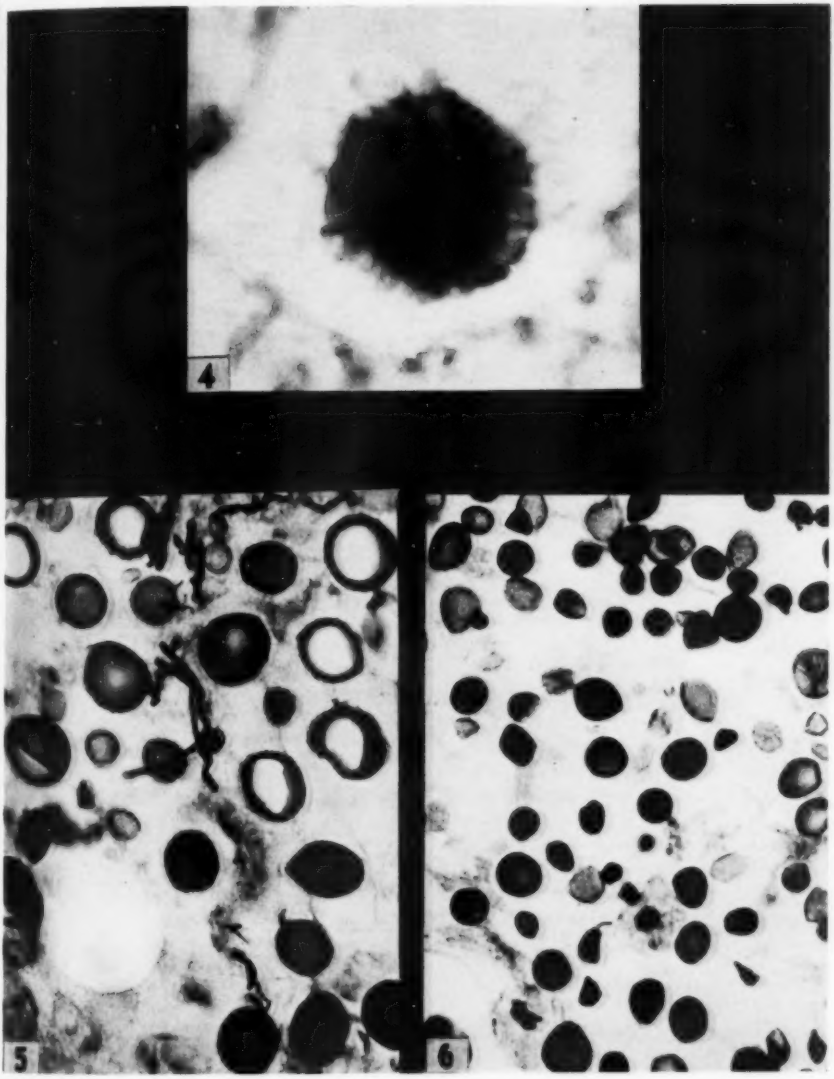
PLATE 2

FIG. 4. Torula cell with surrounding "fur" as demonstrated with Wayson's stain. (× 1200.)

FIGS. 5 AND 6. Torulae contained in cysts in cerebral cortex (same magnification), showing wide variation in the size of the yeast cells. (Di-ammoniacal silver nitrate stain. × 650.)



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GRANULOMATOUS MYOCARDITIS

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Occasional cases of myocarditis offer considerable difficulty in diagnosis. This is true particularly when the lesions resemble those produced by tuberculosis or syphilis. Mönckeberg in his monumental work (1) has remarkably little to say about the latter forms of myocarditis, devoting only 2 pages to tuberculosis and 4 pages to syphilis. Tuberculous myocarditis has been recognized for over one hundred years. Auerbach and Guggenheim (2) have recently reviewed the literature on this subject. The reported cases total slightly less than one hundred. As for syphilis it is now generally recognized that it may cause a true myocarditis (3, 4, 5). The latter is usually seen in the tertiary stage of the disease and is characterized by a widespread diffuse scarring throughout the myocardium with occasional areas of round-cell infiltration. In fresh cases, necrosis of the muscle fibers with associated round-cell infiltration, is found. In such areas spirochetes have sometimes been demonstrated. The differentiation between tuberculous and syphilitic myocarditis may be aided by careful study of the clinical data, including serological and tuberculin reactions, and by the presence of typical lesions in other parts of the body; it may be made decisive either by staining the causative organism in the tissue or by producing the disease in experimental animals.

In the pathological material of the Johns Hopkins Hospital three cases have been found which present severe myocarditis resembling that of tuberculosis or syphilis, but in these cases neither disease can be indicted in spite of studies such as those mentioned above.

CASE I

This case was autopsied in Haiti. Fragmentary notes regarding the gross material were obtained through the courtesy of Dr. T. B. Turner of the International Health Division of the Rockefeller Foundation:

A male negro, aged about 45 years was found dead in the street. There is a

grey mass at the base of the right lung, which has the appearance of an infarct or a new growth. The heart is enlarged, especially the right side. Throughout the wall of the right auricle is a confluent nodular mass. The entire apex of the heart is replaced by a similar nodular mass. The valves are normal. There is marked puckering and scarring of the pulmonary artery, extending into the lungs. The aorta and pericardium seem perfectly normal. One area of liver damage extends about 5 cm. into the substance. The spleen weighs 600 Gm. and its capsule is greatly scarred. The head of the pancreas is very firm and fibrous.

Microscopic Examination

Heart: There is extensive infiltration and in many places entire replacement of the myocardium by a diffuse granulomatous process. The areas most extensively involved contain collections of mononuclear cells (chiefly lymphocytes and monocytes) with occasional eosinophiles and plasma cells, supported by a loose meshwork of connective tissue in which collagen fibrils are plentiful. Numerous thin-walled blood vessels pervade these areas. Scattered through such areas are numbers of small to medium-sized giant cells of the Langhan's type. There is scarcely any tendency toward circumscription or tubercle formation. Some areas are reduced to old hyaline scars practically devoid of cellular elements. In less involved areas the muscle fibers are hypertrophied and have large deeply-staining nuclei. In some places the lesion lies directly beneath the endocardium; in other places it extends outward into the epicardial fat. At one point the media of a small vessel is invaded by the process; at another point the wall of a vessel is nearly destroyed, and its lumen is plugged by thrombi.

Aorta: A process similar to that seen in the myocardium is found in the adventitia and beneath the intima. In places it has frayed apart the medial fibers. Giant cells are rare. There is no perivascular infiltration.

Liver: The same process appears in diffusely scattered foci throughout the liver. The parenchymal cells are greatly shrunken.

Lung: A section from the base of the right lung shows an organizing pleurisy. Directly beneath the pleura is an area replaced by the typical lesion and extending 2.5 cm. into the lung. The former alveoli are filled with a loose granulation tissue containing numerous lymphocytes. A few small giant cells are visible but there is no true tubercle formation.

Spleen: In the entire section the spleen is replaced by the same characteristic tissue.

Special Stains: Numerous sections stained by the Levaditi method showed no spirochetes. Other sections stained by the Ziehl-Neelson and Kinyoun methods showed no acid-fast bacilli.

CASE II[1]

D. H., colored girl, age 6 years. (Harriet Lane Home No. 45821.)
Family History: Non-contributory.

[1] Previously reported by Taussig and Oppenheimer (6).

Past History: Birth normal. Pertussis and streptococcal tonsillitis in infancy.

First Admission to the Harriet Lane Home was at the age of one year because of an acute gastro-intestinal disturbance. The only significant positive finding was enlargement of the spleen. The tuberculin test with 0.1 mg. of tuberculin was negative. X-rays of the extremities showed no evidence of congenital syphilis. The blood Wassermann was negative. A fresh blood preparation showed no sickling of the red blood cells after two hours. At two years of age she developed an acute gonococcal vaginitis.

Second Admission to the Harriet Lane Home was at the age of five years because of acute cervical adenitis and severe anemia. She spent from October 1930 until June 1931 on the wards. Physical examination showed the following positive findings: marked undernutrition, pallor, and icteric sclerae. The heart showed slight enlargement and a soft systolic murmur. The liver and spleen were enlarged—both extending three fingerbreadths below the costal margin.

The red blood cell count was 1,700,000 and the hemoglobin 35% (Sahli). Fresh blood preparations showed immediate sickling of the red blood cells. The leucocyte count was 33,800. The urine examination was negative except for the presence of urobilin. The blood Wassermann was negative. The skin reaction to 0.1 mg. of tuberculin was strongly positive. An x-ray of the chest showed enlargement of the mediastinal nodes. Electrocardiograms were normal. Clinical diagnoses of undernutrition, sickle-cell anemia, and tuberculosis of the mediastinal lymph nodes were made.

Owing to the severe manifestations of sickle-cell anemia, the child was given three transfusions, the mother being used as donor. The first transfusion was given on November 4, the second on December 8, and the third on January 22. These varied in amount from 170 to 300 cc. In an effort to prevent the exacerbations of sickle-cell anemia, the child was treated with intramuscular injections of human serum, obtained from her mother. On March 9 she received 50 cc. in this way, and on May 26 and June 2, 15 cc. In June she was sent home to continue treatment in the dispensary.

Between July 6 and October 10 (inclusive) the patient returned regularly every two weeks and was given 10 cc. of her mother's blood intramuscularly on each visit, 8 injections in all. On November 2 the child developed a widespread papular rash, fever, and general glandular enlargement. Her blood Wassermann reaction was found to be positive. The mother's blood Wassermann reaction had been negative at the beginning of the blood transfusions and injections, but had not been retested subsequently. It was promptly retested and found to be positive.

From November 11 to January 20, 1932, the patient returned regularly for antisyphilitic treatment, receiving a total of 2.5 Gm. of sulpharsphenamine in 9 intramuscular injections. During this period she was afebrile, gained weight and seemed symptomatically better. On January 20 she was admitted to the ward for study of a skin eruption.

Third Admission to the Harriet Lane Home was from January 20 to January 29, 1932, at the age of 6 years. The patient complained only of a mild pruritis and did not appear acutely ill. The skin was covered with myriads of tiny discrete

papules which were brownish and slightly elevated with sunken umbilicated centers. There was pronounced general glandular enlargement. The heart was enlarged to the left and the murmur was of the same character as on previous examinations. The blood pressure was 100/50. The firm smooth liver edge was palpable three fingerbreadths below the costal margin. The spleen was enormously enlarged, extending almost to the level of the anterior iliac spine. The red blood cell count was 3,335,000. The hemoglobin was 50% (Sahli). The leucocyte count was 9,500 with 77% polymorphonuclear cells, 20% lymphocytes, and 3% myelocytes. There was slight sickling in 10 minutes; 70% of the cells showed sickling in 12 hours. The clinical diagnosis was sickle-cell anemia, lichen scrofulosorum, acquired syphilis with healed secondary lesions, and tuberculosis of the mediastinal glands. Immediately after admission the child developed fever ranging between 102° and 104°F. Two days later she developed dyspnoea and acute myocardial failure. The hemoglobin dropped to 25%. The electrocardiogram showed a sinus tachycardia and curves of low voltage (resistance 1800 ohms). Four days later in spite of all therapy she died of cardiac failure. At the time of her death the blood Wassermann was negative. Blood cultures taken five days and one day before death were negative.

Gross Examination: (*Autopsy No. 12399*)

External Appearance: The body is that of an emaciated colored female child, weighing 17 Kg. and measuring 100 cm. in length. There is no edema. The skin shows a generalized eruption which is dry, slightly raised, and of a fine granular character. It is prominent over the suprapubic and cervical regions. The mucous membranes are pale and there is moderate dental caries. There are no external genital lesions.

Abdominal Cavity: The cavity contains about 150 cc. of clear, straw-colored fluid.

Thoracic Cavity: The pleural surfaces are smooth. The pericardial cavity contains about 250 cc. of rather turbid yellow fluid and there are a few fresh fibrinous adhesions near the apex of the heart. The mediastinal lymph nodes are uniformly enlarged, have a yellowish color, and on section show a few small apparently caseous areas.

Heart: The heart is greatly enlarged for a child, weighing 260 Gm. There is a small area of fresh fibrinous exudate near the apex. The surface of the heart everywhere has a diffuse yellow mottling which suggests large deposits of fat. The auricles are only slightly dilated. The valves are all normal, delicate, transparent, and competent. At the apex of the left ventricle are several small mural thrombi. The myocardium of both ventricles is hypertrophied but shows no scarring. The coronary vessels are smooth and patent throughout.

Lungs: The lungs are soft and air-containing except for several collapsed red areas posteriorly. Several small nodules felt in the periphery of the left lung, are found on section to resemble old tubercles. Just beneath the pleura of the right lower lobe is a firm nodule about 2 cm. in diameter. This resembles a primary

tuberculous lesion. The bronchial nodes on both sides are enlarged and yellowish on section.

Spleen: The spleen weighs 175 Gm. and is of a firm, rubbery consistency. The pulp is a uniform brownish-red color. Malpighian bodies are not visible. There are numerous orange flecks scattered through the pulp; in some places they follow the trabeculae.

Stomach and Intestines: The stomach and intestines appear normal. The lymph nodes about the duodenum and pancreas are enlarged.

Other Organs: No lesions are visible.

The heart's blood, pericardial fluid and peritoneal fluid showed no organisms on direct smear and were sterile on culture.

Microscopic Examination

Heart: Throughout the myocardium of ventricle and auricle is a dense, diffuse infiltration with mononuclear cells. The muscle fibers have been completely destroyed in places and at a few points there are definite areas of caseation around which monocytes and even giant cells are seen. The pericardium and epicardium are thickened and at one point in the wall of the right ventricle there is a mural thrombus. Very little normal myocardium is seen. The fibers remaining are hypertrophied.

Lungs: Numerous tubercle-like lesions are scattered throughout both lungs. These consist of epithelioid cells, a few giant cells, and in some places, centers of slight necrosis. A few of these lesions lie directly beneath the intima of the blood vessels but show no tendency to break through into the lumina.

Bronchial and Retroperitoneal Lymph Nodes: Here are found the same tubercle-like lesions, necrosis being rather prominent. Section of the peritracheal node shows an old caseous area with powdery calcification.

Spleen: The blood spaces are dilated, the malpighian bodies are rather small and for the most part are surrounded by lakes of blood giving the appearance so typical of sickle-cell anemia. No tubercle-like lesions are seen.

Liver: There is atrophy of the cells in the central parts of the lobules with corresponding widening of the sinusoids. There are numerous areas of focal necrosis with giant cells, and there is round cell infiltration in the periportal regions.

Kidneys, Pancreas, Adrenals, Tonsils, Rib: No lesions are seen.

Bone Marrow: Marrow of the ribs, femur, and vertebrae is definitely hyperplastic.

Skin: A section from the skin of the abdomen shows occasional accumulations of lymphocytes directly beneath the derma and about the coil glands. At no point is the epithelial layer actually broken.

Special Stains: Sections stained by the Levaditi, Fontana, and Krajian modification of Dieterle's methods show no spirochetes. No acid-fast organisms are demonstrable by the Ziehl-Neelson or Kinyoun methods.

Anatomical Diagnosis: Sickle-cell anemia with the splenic changes characteristic of this condition; hyperplasia of the bone marrow; tubercle-like coalescent

areas with necrosis and giant cells throughout the myocardium, liver, lungs, and lymph nodes; focal accumulations of lymphocytes beneath the skin; cardiac hypertrophy and dilatation; mural thrombus, left ventricle; sero-fibrinous pericarditis; chronic passive congestion of the liver; ascites; calcified bronchial lymph node.

CASE III

M. D., a colored female, 24 years old. (Unit No. 64680.)

Family History: A maternal grandmother had been given "needle treatments" 3 times a week for one year several years before.

Past History: In childhood the patient had had pertussis, mumps, measles, influenza and probably pneumonia. She had had occasional sore throats, but denied ever having had rheumatism, gonorrhoea or syphilis. She had been married 12 years but had never been pregnant. During the 4 months before admission she had lost 20 lbs. in weight but did not recall having had any fever.

Present Illness: For several months before admission she had experienced dyspnoea and palpitation after walking 3–4 blocks. One week before admission, while walking on the street she had suddenly fainted. Upon regaining consciousness she found that her heart was beating extremely rapidly, but she had no precordial distress. Frequent vomiting and tachycardia lasted for about 24 hours, then ceased, leaving her comfortable but weak. On the day before admission she had another similar episode. September 8, 1935 she was admitted to the Medical Service.

Physical Examination: Temperature 100.8° F. (rectal); pulse 230; respiration 38; B.P. 90/70. The patient was drowsy, apathetic, but well oriented. There were several palpable cervical nodes but no general glandular enlargement was evident. The tonsils were large and scarred but showed no active inflammation. Examination of the lungs was negative except for occasional subcrepitant inspiratory râles at the right base posteriorly, as high as the axilla. The heart was definitely enlarged to percussion: 11 cm. to the left and 3.5 cm. to the right. The very rapid regular rhythm made the detection of murmurs impossible. Neither changes in position nor vagal pressure affected the rate or rhythm. The radial pulses were scarcely perceptible. The peripheral vessels showed no sign of sclerosis. The liver edge was not palpable. There was no edema. The vagina contained a milky white discharge and there was some tenderness and induration in the right adnexal region.

Laboratory Data: Blood: Hgb. 88% (Sahli), R.B.C. 4,600,000, W.B.C. 15,200, polymorphonuclears 71%, lymphocytes 25%, monocytes 4%. A catheterized specimen of urine showed 5 white cells per high-power-field and contained a slight trace of albumen. The blood Wassermann and flocculation tests were negative. A teleoroentgenogram of the heart showed definite enlargement; M.R. 3.8 cm., M.L. 10.2 cm., A. 4.3 cm., T. 24.3 cm. A roentgenogram of the chest was interpreted as showing beginning consolidation in the right lung. A urine culture grew B. alkaligenes, B. coli, Alpha streptococci, and nonhemolytic staphylococci. The venous pressure was 110 cm. of water. The blood non-protein nitrogen was

30 mg. per 100 cc.; total plasma protein was 6.6 gm. per 100 cc. A stool examination was negative. The basal metabolic rate was −5. Tuberculin tests with as much as 0.1 mg. intracutaneously, were negative.

Course: The patient was given calcium chloride intravenously and acetyl beta-methyl choline without any effect upon the cardiac rate. On the second day quinidine sulphate was started and after 1.3 Gm. had been given the heart rate dropped to 110 per minute. Thereafter the pulse varied between 80 and 90. An electrocardiogram showed a P-R interval of 0.16 sec., Q.R.S. duration of 0.08 sec. There was right ventricular preponderance. The temperature varied between 100° and 103.2° (rectal) for 4 days, thereafter was normal. A roentgenogram taken on the sixth day showed "apparent regression of the consolidation in the midportion of the right lung." Fluoroscopy showed increase in the size of the upper mediastinal glands. On the sixth day the following note was made: "The sounds at the apex are faint. There is marked accentuation of the second sound at the pulmonic area. When the patient sits erect there is a soft systolic murmur over the entire precordium." The heart rate remained regular and the patient was discharged, comfortable and ambulatory on September 26th, 1935 with instructions to take 0.1 Gm. of quinidine sulphate, 4 times daily.

She was seen in the medical dispensary at fortnightly intervals, took 0.1 Gm. of quinidine sulphate twice daily and was able to do her housework without any discomfort. On the evening of February 20, 1936, while playing cards, she suddenly became dyspnoeic, cried out, lost consciousness and died while being taken to the hospital.

Gross Examination: (Autopsy No. 14657)

External Appearance: The body is that of a young colored female, measuring 154 cm. in length and weighing 56.5 Kg. Nutrition is good; there is no edema. There are no wounds, ulcers or eruptions of the skin. The face and head are normal. There are no external genital lesions.

Abdominal Cavity: There is no free fluid or gas. The peritoneal surfaces are smooth.

Thoracic Cavity: The pleural cavities have smooth surfaces and contain no fluid. The pericardial cavity contains 40 cc. of straw-colored fluid. Its surfaces are smooth.

Heart: The heart weighs 330 Gm. and its left ventricle is dilated. There is one old fibrous patch in the epicardium of the right ventricle. The external surface of the left ventricle presents a most peculiar appearance. Yellowish-grey areas, bulging a trifle above the surrounding myocardium occupy most of the region. These have hyperemic red borders and the overlying epicardium is slightly roughened. There is a patch of old fibrous adhesions at the apex. A few thin white plaques are found beneath the endocardium of the right ventricle. The valves are all delicate and of normal measurement.

On section the anterior apical and posterior wall of the left ventricle, as well as portions of the papillary muscles and interventricular septum show an extra-

ordinary series of irregularly-shaped lesions somewhat resembling patches of yellowish-grey cheese. These areas have hyperemic red borders, and are somewhat firmer in consistency than the surrounding myocardium. Their cut surfaces are finely granular yet not friable. In places the wall is quite normal. The auricles are unaffected by the process. The coronary vessels are smooth throughout and show no sclerosis or narrowing. The great vessels are normally arranged. The formen ovale is closed and the ductus arteriosus is obliterated.

Lungs: The pleural surfaces of both lungs are smooth but beneath them numerous small grey flecks or nodules less than 1 mm. in diameter shine through. These are particularly prominent along the medial surface of the right lower lobe, and section here shows a little patch of rather diffuse consolidation. In the right middle lobe there are a few small grey areas suggesting caseous tuberculous lesions. Nowhere are these confluent or excavated. A pulmonary vein in the right lower lobe shows numerous tiny tubercle-like nodules beneath the intima. Elsewhere the lungs are air-containing and brick-red in color with occasional minute grey patches. No apical lesions are observed.

Lymph Nodes: About the bifurcation of the trachea there are numerous enlarged nodes which bulge well into the interlobar fissures of both lungs. They are discrete, firm, grey, and portions of them are anthracotic. The largest node measures 6 × 4 × 3.5 cm. They show neither calcification nor caseation. Patchy areas of similar firm, greyish material are found in several smaller cervical lymph nodes. None of the retroperitoneal or mesenteric nodes measures more than 1 cm. in diameter but several of them present the same picture as the larger intrathoracic ones.

Spleen: The spleen weighs 160 Gm. Its capsule is smooth, the pulp rusty-red in color, and the grey malpighian bodies are very prominent.

Liver: The liver weighs 1575 Gm. No lesions are visible grossly.

Pancreas, Stomach, Intestinal Tract, Kidneys, Adrenals, Neck Organs, Blood Forming Tissues, Brain, Meninges, and Hypophysis: No lesions are seen.

Aorta: The intimal surface is smooth; a few yellowish plaques appear toward the lower end of the vessel.

Pelvic Organs: There are numerous old adhesions about the fallopian tubes and ovaries. One ovary contains a small cyst filled with clear fluid.

Microscopic Examination

Heart: Large areas of the myocardium are replaced by a compact granulation tissue which is heavily infiltrated with lymphocytes, monocytes, and plasma cells. In some places this tissue is quite vascular. There are fairly well circumscribed areas that have the appearance of accumulations of loose tubercles. Some of these contain one or more Langhan's giant cells. Caseation is present but not conspicuous. There are areas in which the dead tissue is hyalinized. The myocardial fibers are considerably hypertrophied.

Lung: The parenchyma is studded with numerous tubercle-like lesions. Most of them are rather small, and like those in the myocardium, show little tendency

toward caseation. They contain one or more Langhan's giant cells and are surrounded by thin zones of granulation tissue heavily permeated by lymphocytes, monocytes and plasma cells. A number of these lesions are found in the walls of blood vessels and bronchi. No points of actual rupture are found. Similar lesions are found directly beneath the pleural surface, and in this situation they show a marked tendency to become confluent. In one region the lung structure is practically obliterated by subpleural lesions, and numerous new thin-walled vessels are found. In other sections the alveoli contain many desquamated epithelial cells and monocytes.

Bronchial Lymph Nodes: These nodes are entirely replaced by tissue similar to that found in the heart and lungs. Many of these lesions are hyaline.

Spleen: The malpighian bodies are small but numerous. No lesions are seen.

Liver: There are small focal accumulations of lymphocytes throughout the liver, most of them occurring in the periportal regions. One of them contains a bit of granulation tissue and somewhat resembles the pulmonary and myocardial lesions, although no giant cells are present.

Ovary: The cyst is of typical follicular appearance.

Other Organs: No lesions are found.

Special Stains: No spirochetes are found in sections stained by the Levaditi method. No acid-fast organisms are demonstrated by Ziehl-Neelson or Kinyoun methods.

Animal Inoculations: Cultures from the bronchial nodes were sterile. Fresh material from these nodes was thoroughly ground in a sterile mortar, suspended in normal salt solution, and injected into the testes of two rabbits, and into inguinal regions of two guinea pigs. These animals gained weight, appeared perfectly healthy, and when killed and autopsied six months later, showed no lesions whatsoever.

Anatomical Diagnosis: Myocarditis of unknown etiology with tubercle-like lesions and mononuclear infiltration; similar lesions in lungs, peritracheal and bronchial lymph nodes; focal accumulations of lymphocytes in liver; salpingitis, chronic, bilateral; cyst of right ovary.

To recapitulate, three cases have been described, all of them having extensive, severe granulomatous myocarditis, with involvement of numerous other organs in a similar granulomatous process. Two of the cases died in acute myocardial failure; death in the third case was sudden and did not occur while the patient was under observation. The histological picture in all three cases was characterized by a diffuse granulomatous process containing giant cells and showing a tendency toward tubercle formation. There was slight disposition toward caseation. Necrosis of tissue with replacement by collagen and resultant scarring, was common to all. Also common to all was

the involvement of the vessel walls by focal subintimal lesions unlike the perivascular lesions of syphilis. The lesions did not resemble those of rheumatism and no Aschoff bodies were found. Despite their rarity, syphilitic and tuberculous myocarditis were the conditions which these cases brought to mind.

Concerning a syphilitic etiology for these lesions: In *Case I* the lack of sufficient clinical data precludes discussion from this standpoint. Pathologically there was complete absence of the extracardiac lesions usually associated with syphilis. No true perivascular accumulations of round cells were evident. No spirochaetes could be demonstrated by any method. In *Case II* although the child acquired syphilis, the heart is known to have been definitely enlarged, and a systolic murmur was noted on many occasions prior to the inoculation with the infected mother's blood. Numerous attempts to stain spirochetes by various methods were unsuccessful. In *Case III* the blood Wassermann and flocculation tests were repeatedly negative. Spirochetes could not be demonstrated in any of the organs in spite of numerous attempts. And finally injection of material from the fresh typical lesions into rabbit testes failed to produce any lesions in the experimental animals.

Tuberculous myocarditis (2) may occur in miliary form, as isolated large nodules sometimes spoken of as "conglomerate tubercles," or in a diffuse form, with or without caseation. Concerning a tuberculous etiology for these cases: in *Case II* the intracutaneous tuberculin test with 0.1 mg. was positive. In *Case III* a similar tuberculin test was negative. In spite of their enormous size the peritracheal lymph nodes were discrete and separate; adhesions and matting together did not occur. In none of these cases could acid-fast organisms be demonstrated although acid-fast bacilli were readily demonstrated in controls in which known tuberculous tissues were stained by means of the same solutions. Finally, injection of material from the typical lesions into guinea pigs failed to produce any lesions.

For consideration there yet remains a group of cases which have been reported under various names—"circumscribed myocarditis," "interstitial myocarditis," "idiopathic myocarditis"—and generally referred to as "Fiedler's myocarditis." This condition (7) is described as a rapidly progressive myocardial failure ending in death

and showing at autopsy a diffuse interstitial infiltration of the myocardium with polymorphonuclear and mononuclear leucocytes. Giant cells have been described in these cases, but never tubercle formation. No causative organism has ever been demonstrated. The condition is not to be confused with the acute myocarditis occurring during the course of pyogenic infections, acute respiratory infections, and severe burns. Over 30 cases of *Fiedler's myocarditis* are on record in the literature (8). The cases here reported differ from *Fiedler's myocarditis* in the overwhelming predominance of mononuclear cells, and in the presence of tubercles. In none of the published photographs of *Fiedler's myocarditis* do the lesions resemble those in the present cases.

Under the name of *myocarditis perniciosa*, Boikan (9) has described a single case of rapidly progressive fatal myocarditis occurring in a white woman of 28 years. Briefly, the autopsy findings were: dilatation and hypertrophy of the heart with mural thrombi in the left ventricle and right auricle, thrombosis of the femoral veins, old and recent infarcts in both lungs, chronic passive congestion of the remaining organs, and generalized edema. The myocardium was extensively infiltrated with leucocytes, predominantly lymphocytes. Fibrin was evident in the fresher lesions throughout the myocardium, and there was marked scarring with formation of new vessels. A similar case was described by Miller (10). Pathologically the findings in the present cases differ from those of "myocarditis perniciosa" in the tendency toward tubercle formation, the presence of giant cells, and the presence of lesions in other viscera.

Boeck's sarcoid may ocasionally involve the myocardium. Such a case has been reported by Nickerson (11). The sarcoid lesions as described by Longcope and Pierson (12) are essentially collections of "large palely staining cells arranged in the form of miliary tubercles, sometimes lying as isolated structures in a comparatively normal tissue, and sometimes occurring in groups or strands." They are not, as a rule, outlined by an inflammatory zone of lymphoid cells, though in some cases this may occur. In some instances there are a few necrotic cells in the tubercles, but the absence of caseation has attracted the attention of almost everyone who has written on the subject. A case recently autopsied in this department and soon to be reported shows such lesions throughout the myocardium. In cases I and II

under consideration, the marked inflammatory reaction about the lesions, and especially the tendency toward caseation, speak against the diagnosis of sarcoid. Case III exhibits less inflammatory reaction and caseation, and may possibly represent sarcoid.

Finally there have been two cases of "granulomatous myocarditis" in this department which may be described briefly because of a certain similarity to the three cases reported above.

CASE IV

C. F., a colored female of 27 years (Unit No. 64680), was first admitted to the hospital on April 21, 1932 with symptoms of hypertension of two years duration. For one week she had shown marked myocardial failure. Examination showed generalized edema, vascular retinitis, albuminuria, and enlargement of the liver. She was treated by digitalis and bed rest, improved considerably, and was discharged on June 11, 1932.

She was admitted to the hospital on March 1, 1933 with signs and symptoms of mild myocardial failure. Examination showed an enlarged heart with gallop rhythm, albuminuria, blood non-protein nitrogen of 88 mg. per 100 cc., and phthalein excretion of 5% in two hours. After treatment with diuretics she improved and was discharged on April 2, 1933.

Her third admission was on April 13, 1933 because of the return of myocardial failure and the appearance of uremia. The blood pressure was 230/140, the blood non-protein nitrogen 144 mg. per 100 cc., and the blood Wassermann negative. Hgb. 7.2 Gm. (Sahli), R.B.C. 3,200,000, W.B.C. 11,000. The urine contained albumin, white blood cells and occasional hyaline casts. Temperature, pulse and respirations were normal. In spite of treatment she died on May 1, 1933.

Gross Examination: (Autopsy No. 13127)

Heart: The heart weighs 585 Gm. The enlargement is due chiefly to hypertrophy and dilatation of the left ventricle. The pericardium over the anterior surface of the left ventricle is thickened and roughened. Small grey flecks suggesting scars are found throughout the myocardium of both ventricles. The endocardium and valves are normal. The coronary vessels show occasional small sclerotic patches.

Lungs: There are small scars at the apices of both lungs. Throughout the lung parenchyma are sparsely-scattered minute dots which may represent miliary tubercles. No other lesions are seen.

Lymph Nodes: The mediastinal lymph nodes are considerably enlarged, grey in color, and firm in consistency. At the hilum of the right lung are several nodes, the largest measuring 5 × 3 × 2 cm. This is soft in consistency and on section shows many yellow flecks embedded in the grey tissue. Large nodes about the head of the pancreas as well as the cervical nodes are of similar appearance.

Spleen: The spleen weighs 145 Gm. and shows no lesions.

Liver: The liver weighs 1855 Gm. Its superior surface is roughened and shaggy owing to adhesions which bind it to the diaphragm. It is very pale and on section shows numerous minute grey spots. Chronic passive congestion is slight.

Kidneys: The left kidney weighs 180 Gm. and right 150 Gm. Their surfaces are granular. On section the cortex is found to be somewhat reduced in width. The striae for the most part are obliterated and throughout the cortex there are numerous small punctate hemorrhages.

Bladder: The mucosa is reddened and rather granular in appearance. There is some edema about the ureteral orifices.

Aorta: The aorta is elastic and of normal calibre. It contains a few scattered sclerotic plaques.

Other Organs: No lesions are visible except those mentioned in the anatomical diagnosis.

Microscopic Examintion:

Heart: The myocardium is quite scarred and shows many foci of lymphocytic and monocytic infiltration. Polymorphonuclear cells are rare but are found in one area of focal necrosis which also contains a few Langhans' giant cells. Other areas suggest loose poorly-defined tubercles. Many of the muscle fibers are shrunken or altogether atrophied. Elsewhere the mononuclear cell infiltration is more diffuse and occupies large areas. None of the lesions resemble Aschoff bodies. At one point the epicardium shows fibrous thickening but none of the typical lesions involve either epicardium or endocardium.

Lungs: Small areas of organizing hemorrhage are evident throughout. Numerous small lesions resembling miliary tubercles are found. They consist of one or more giant cells surrounded by epithelioid cells and many lymphocytes and monocytes. Necrosis is found in a few of them but no caseation is present.

Lymph Nodes: Sections from mediastinal, cervical, and retroperitoneal nodes show almost complete replacement of lymphoid tissue by lesions similar to those found in myocardium and lungs. Here the lesions are larger and scarring is much more conspicuous. Many of the older lesions are hyaline. Necrosis and slight caseation are present in the centers of some of the lesions.

Spleen: No abnormalities are evident.

Liver: There is widespread atrophy of the central cells of the liver lobule. Here and there are minute tubercle-like lesions similar to those seen in the heart and lungs.

Kidneys: Great destruction of renal parenchyma and scarring are found throughout. The characteristic feature of this nephritis is a solidification of the glomerular tufts which have been converted into hyaline masses often loaded with globules of fat. The glomerular capsules are thickened but no exudates are seen. Many of the tubules are collapsed while others are dilated and contain casts and leucocytes. The pelvis contains numerous polymorphonuclear cells and lymphocytes. Cortex and medulla are heavily infiltrated with lymphocytes but no tubercle-like lesions are found.

Bladder: There is widespread subepithelial infiltration by lymphocytes and occasional polymorphonuclear cells. The muscularis is not involved.

Uterine Tubes: Sections from both tubes show marked thickening of the villous folds and numerous adhesions binding one fold to another.

Aorta: There are some fat deposits beneath the intima. At one point a small knob projects into the lumen of the vessel. This consists of tubercle-like lesions covered completely by endothelium.

Thyroid: In one area there is a small encapsulated adenoma. Near this are several of the typical lesions described above.

Other Organs: No lesions are found except those mentioned in the anatomical diagnosis.

Special Stains: No spirochetes are found in sections stained by the Levaditi method. No acid-fast organisms are demonstrated by Ziehl-Neelson or Kinyoun methods.

Anatomical Diagnosis: Peculiar infection with tubercle-like lesions and mononuclear infiltrations in myocardium, aorta, liver, lungs, thyroid, and lymph nodes; chronic glomerulonephritis; history of hypertension; cardiac hypertrophy and dilatation; pericardial adhesions; slight chronic passive congestion; chronic pyelitis and cystitis; areas of organizing hemorrhage in lungs; areas of hemorrhage in liver; myomata uteri; chronic salpingitis, bilateral; fibrous adhesions between liver and diaphragm; slight generalized arteriosclerosis; small adenoma of thyroid.

Comment: That the peculiar lesions found in this case are not tuberculous is clear from the fact that the spleen contains none. In miliary tuberculosis the spleen invariably contains tubercles when the liver does. The lesions might be regarded as syphilitic but the Wassermann reaction was negative on repeated tests and the intimal involvement of the aorta without lesions in the media speaks against a syphilitic etiology.

CASE V

B. B., a colored male of 56 years (Unit No. 45883), was admitted on October 17, 1932 complaining of nervousness. His past history and family history were essentially negative. Six months before admission the patient had had influenza followed by tremor, nervousness, cough, sweating, increased appetite, and palpitation. Within three months he had lost 40 lbs. in weight. On admission his temperature was 98.6° F., pulse 130, respirations 26, and blood pressure 150/80. He showed emaciation, restlessness, tremor, prominent eyes, and a moderately enlarged thyroid with a loud bruit. The blood Wassermann was negative. The basal metabolic rate was plus 71. R.B.C. 4,300,000, Hgb. 11.2 Gm. (Sahli), W.B.C. 7,200 with a normal differential. Urine examination was negative. After 18 days rest in bed and medication with phenobarbital the basal metabolic rate was plus 55. He was then given Lugol's solution for 9 days but started running a fever of 100° to 102°. Potassium iodide was substituted for Lugol's solution but after 2 days of this medication he developed a fever of 104°, coryza, rash, pains in the joints, malaise, inflamed pharynx, and a hemorrhagic stomatitis.

The iodide was discontinued, but the pulse rate rose to 200, the chest filled with coarse râles and rhonchi, and the patient died on November 25, 1932. The clinical diagnoses were: exophthalmic goiter, sensitivity to iodine, exacerbation of hyperthyroidism following withdrawal of iodine, dermatitis medicamentosa.

Gross Examination: (Autopsy No. 12880)

Skin: Almost the entire skin is covered with a desquamating macular rash.

Heart: The heart weighs 330 Gm. Small patches of fat are visible through the myocardium and a few minute scars are seen. The endocardium and epicardium are normal. The valves are delicate and competent. In places the coronary vessels are narrowed by sclerosis but at no point are they occluded.

Lungs: There are old scars at the apices of both lungs. The cut surfaces are moist, dull red in color and air-containing throughout except in a few small areas of recent hemorrhage. The bronchi and bronchioles are all fiery red in color and show little grey patches of exudate.

Lymph Nodes: The axillary and inguinal nodes are considerably enlarged. Accumulations of nodes, matted together, measure as much as 8 x 5 x 4 cm. These nodes are dull grey in color and are studded with small hemorrhages.

Liver: The liver weighs 1620 Gm., is flabby and soft. Its surface is smooth. No lesions are seen on section.

Spleen: The spleen weighs 370 Gm. There are areas of yellowish discoloration beneath the capsule. The cut surface bulges, is deep red in color, and the malpighian bodies are large and quite conspicuous.

Stomach and Intestines: The rugae of the stomach are smoothed out and flecked with small hemorrhages. No lesions are seen in the intestines.

Pancreas: The organ weighs 40 Gm. and is dull grey in color.

Bladder and Ureters: The mucosa is flecked with minute hemorrhages.

Neck Organs: The tonsils are large and reddened with fresh fibrinous exudate. Small amounts of purulent material are expressed from the crypts. The mucosa of the larynx and trachea is fiery red and spotted with small flecks of grey exudate. Both lobes of the thyroid are moderately enlarged, each measuring 6.5 x 3.5 x 3 cm. Its tissue is firm in consistency and on section shows many small yellow opacities. The thymus weighs 45 Gm.

Aorta: The vessel has lost a good deal of its elasticity. Numerous sclerotic patches are seen throughout its length.

Other Organs: No lesions are seen.

Microscopic Examination:

Miliary Inflammatory Nodules: In most of the tissues there are peculiar, rather circumscribed, focal inflammatory lesions, differing from each other very little in their essential features. They consist of a central focus of necrosis, and often a giant cell of the Langhans' type, surrounded by poorly-defined epithelioid cells, the whole permeated by leucocytes, chiefly lymphocytes, plasma cells and eosinophiles. Some of the lesions, particularly those in the spleen and lymph nodes are

caseous. Many of them suggest miliary tubercles in appearance. Others are less well defined and resemble only non-specific granulation tissue.

Skin: Besides the focal nodules already described, the derma contains a diffuse infiltration of mononuclear cells. This extends well around the hair follicles and sebaceous glands. At some points the epithelium is ulcerated, at others there is marked desquamation.

Heart: In the myocardium of both right and left ventricles are numerous small scars as well as many of the focal lesions. One papillary muscle is replaced by these lesions. The epicardium and endocardium are intact.

Lungs: The bronchioles are filled with purulent exudate and are considerably distended. In a few regions the alveoli are filled with fresh hemorrhage. A few of the typical lesions are found about the larger bronchioles.

Lymph Nodes: All of the lymphoid tissue is markedly hyperplastic. The blood vessels are dilated and the sinuses filled with mononuclear cells. The typical lesions are found in abundance and show considerable caseation. Many of them are large and occupy the position of the germinal centers.

Liver: The periportal regions are densely infiltrated with mononuclear cells of all types. The typical lesions seem to lie chiefly about the hepatic arterioles, and radiating from them are fringes of epithelioid cells. Eosinophiles are particularly common. The hepatic cords appear normal.

Spleen: In addition to the circumscribed nodules which occupy chiefly the malpighian bodies, there are numerous small necrotic areas lying directly beneath the capsule. In places these thin zones of necrosis lie along the trabeculae, extending deeply into the interior. Many of these are surrounded by epithelioid cells. Numbers of large monocytes, characteristic of acute splenic tumor, are found throughout the pulp. Small hemorrhages are evident throughout.

Stomach: A few of the inflammatory nodules are found in the submucosa.

Bladder and Ureters: There are numerous little focal accumulations of leucocytes about the blood vessels. These are not as well circumscribed as the lesions elsewhere and eosinophiles are quite numerous.

Kidneys: The typical lesions are quite widespread throughout cortex and medulla. Numerous lymphocytes and plasma cells lie beneath the pelvic epithelium.

Thyroid: There is well marked epithelial hyperplasia. Lymphoid tissue is plentiful and a few of the typical lesions are found beneath the capsule.

Thymus: The lobules of lymphoid tissue are fairly large. The Hassall bodies are prominent and for the most part, necrotic.

Tonsils: The crypts contain polymorphonuclear leucocytes and compact masses of fibrin. They also contain large colonies of bacteria which prove to be staphylococci. In places the epithelium is ulcerated and covered with fresh exudate. The vessels are distinctly engorged.

Prostate: The organ contains a few of the focal lesions but the intervening tissue is normal.

Aorta: The adventitia is slightly thickened. In the media there are numerous

little foci of necrosis, surrounded by small accumulations of lymphocytes, monocytes, and a few eosinophiles. An elastic tissue stain clearly shows the interruption of the medial elastic fibers.

Other Organs: No lesions are seen.

Special Stains: No spirochetes are found in sections stained by the Levaditi method. No acid-fast organisms are demonstrated by Ziehl-Neelson or Kinyoun methods.

Anatomical Diagnosis: Hyperplasia of thyroid; enlargement of thymus; scars in myocardium; peculiar miliary lesions consisting of necrosis and mononuclear and eosinophile infiltration, in skin, myocardium, lungs, lymph nodes, spleen, liver, kidneys, aorta, prostate, stomach, and ureters; acute splenic tumor; acute tonsillitis; purulent bronchitis; hemorrhages in lungs; scars in pleura.

Comment: The skin lesions in this case are particularly striking and probably the result of iodine sensitivity. However, the essential microscopic lesion is similar to that observed in the previous cases although the infiltration of eosinophiles is more conspicuous in the present case

SUMMARY

Five cases are described in which the myocardium and other tissues were involved in a granulomatous process characterized by tubercle-like foci with giant cells, necrosis, and mononuclear cell infiltration. There was no evidence in support of a tuberculous or syphilitic etiology. In one case in which animal inoculation of material from the lesions was carried out the results were negative.

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EXPLANATION OF ILLUSTRATIONS

(*Photographs by Mr. Milton Kougl*)

FIG. 1. Replacement of myocardium by granulomatous lesion. Case I.
FIG. 2. Giant cells in lesion in Case I.
FIG. 3. Heart of Case II, showing mottling of myocardium due to lesions.
FIG. 4. Lesion in myocardium showing tubercle-like nodules. Case II.

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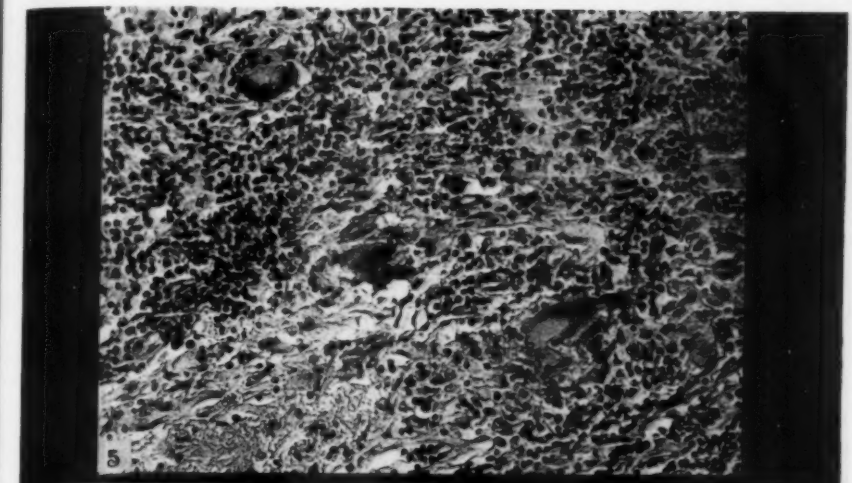
EXPLANATION OF ILLUSTRATIONS

(Photographs by Mr. Milton Kougl)

FIG. 5. Lesion in myocardium in Case II showing mononuclear and giant cells.
FIG. 6. Heart in Case III, showing gross appearance of lesions.
FIG. 7. Myocardial lesion in Case III.
FIG. 8. Giant cell in lesion of Case III.



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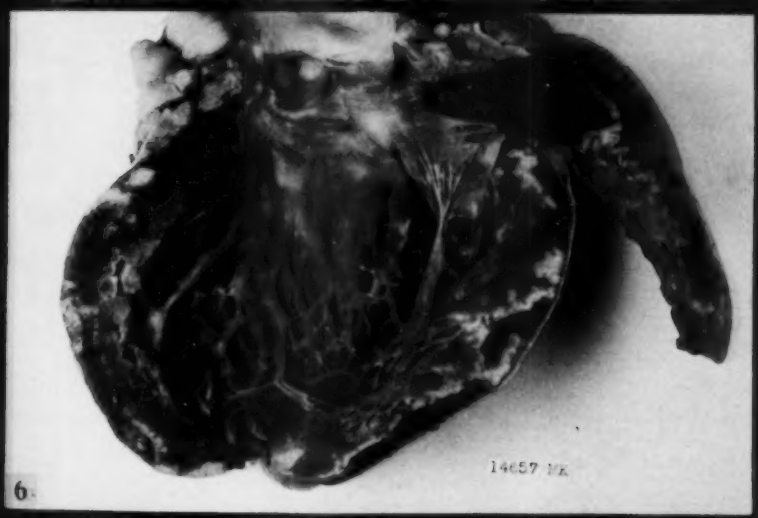

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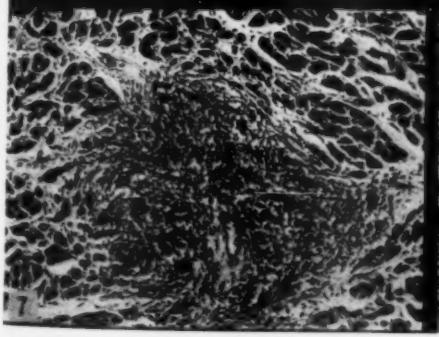

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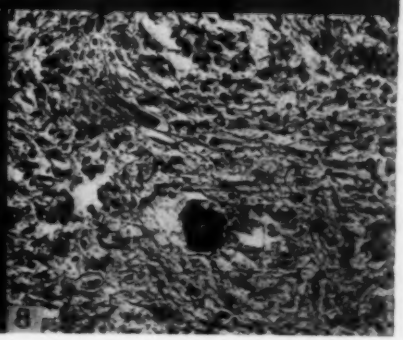

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A PRELIMINARY REPORT OF THE PROPHYLACTIC USE OF SULFANILAMIDE IN PATIENTS SUSCEPTIBLE TO RHEUMATIC FEVER

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There is much evidence pointing to the association of beta hemolytic streptococcal infections with attacks of rheumatic fever (1, 2). Recently, sulfanilamide (para-amino-benzene-sulphonamide) has been shown to have a prophylactic action upon beta hemolytic streptococcal infections in mice (3) as well as a therapeutic effect on such infections in both laboratory animals and man (4, 5, 6). It seemed important to ascertain whether sulfanilamide might prevent the occurrence of rheumatic recrudescences in susceptible patients by controlling the antecedent streptococcal infections.

The difficulties of the problem are apparent. In order to ascertain the efficacy of sulfanilamide in the prevention of rheumatic fever, carefully controlled observations must be made on a large series of patients in different parts of the country over a number of years. The purpose of this paper is to call attention to a possible beneficial rôle of sulfanilamide, to state briefly our experience with a group of patients who have taken the drug continuously between November and June during the past two winters, and to outline a plan which has proved useful to us in studying the problem.[1]

SELECTION OF PATIENTS

Patients for the therapeutic experiment were chosen from the Cardiac Clinic of the Department of Medicine of this hospital. Each

[1] We have studied only the prophylactic use of sulfanilamide; the therapeutic effect of sulfanilamide in acute rheumatic fever, which has recently been reported upon unfavorably by several authors, has not been considered in this paper.

had suffered from acute rheumatic fever[2] within three years, and was considered liable to further recrudescences.

During the first winter, 1936–37, since the number of patients was small, it seemed preferable to give the entire group sulfanilamide in order to obtain a rough estimate of its effectiveness, rather than to subdivide the patients into therapeutic and control groups. Actually, 18 of those chosen proved coöperative, and the remaining seven afforded a small control series. During the winter of 1937–38, 19 patients received sulfanilamide; seven of these had been in the original treated group. Twelve new controls were added, and the 11 patients who received treatment the first winter, but not the second, formed a control group of a different type. The patients ranged in age from 14 to 36 years; the distribution by decades was

TABLE I

Age Distribution by Decades of Treated and Control Cases

AGE	GROUP TREATED WITH PABS*	CONTROLS THAT HAD NEVER RECEIVED PABS	CONTROLS THAT RECEIVED PABS THE WINTER BEFORE	TOTAL CONTROL GROUP
14–19	17	13	5	18
20–29	7	2	4	6
30–36	6	4	2	6
Total.....	30	19	11	30

* PABS = para-amino-benzene-sulphonamide.

similar in the treated and untreated groups (Table I). Since no patients under 14 were available in the Department of Medicine, we have no information concerning the prophylactic use of sulfanilamide in childhood.

HISTORY OF RHEUMATISM

Every patient had had one or more "major rheumatic episodes," the last one occurring within three years of beginning treatment (figure 1). A *major episode* is defined as one in which the patient is ill enough to be confined to bed at home for at least a week or to be hospitalized, and in which fever, polyarthritis, active carditis, chorea or other signs are unequivocal. Outspoken chorea is considered a

[2] Not necessarily the first attack.

major episode only when the patient affected had had other forms of rheumatic fever as well. A *minor episode* signifies a definite but less incapacitating form of rheumatic fever such as transiently painful, swollen joints or mild choreiform movements. A *questionable episode* includes any major or minor illness in which the diagnosis of rheumatic fever is in doubt, as well as such isolated symptoms as epistaxis, sore throat, arthralgia or precordial pain in a rheumatic individual.

We shall not discuss the cardiac lesions of the patients in detail, as it does not seem pertinent to this paper. Almost all of the patients had rheumatic endocarditis; a few were classified[3] as having potential heart disease. Of those with organic disease, the majority were able to carry on ordinary physical activity without discomfort (Class 1). Four or five patients had to limit their activities slightly (Class 2 a). None were greatly limited in activity, so that none of the group fell into Class 2 b or Class 3.

ADMINISTRATION OF SULFANILAMIDE

Dosage: 15 grains of sulfanilamide daily divided into three doses were prescribed from November 1936 to June 1937. Nine of the 18 patients were on a single dose of 5 grains daily at first, but this was increased to the routine dose within a few weeks. During the second winter the dosage was increased to 20 grains daily divided into two doses, and was given from October 1937 to June 1938.

Frequency of Visits and Continuity of Treatment: The patients receiving sulfanilamide were seen in the Cardiac Clinic at three week intervals throughout the period of treatment. Patients in the control series were seen less frequently. In general, the continuity of treatment was good, although a few patients reported short periods when the drug was not taken for various reasons.

Concentration of Sulfanilamide in the Blood: Determinations of the concentration of sulfanilamide in the venous blood were begun in April 1937 and were made at each visit during the winter of 1937–38. The method of Marshall (8) was used. When 15 grains of the drug were taken daily in three divided doses the concentration of the drug in the blood usually fluctuated between 1.0 and 3.0 mg. per 100 cc.

[3] Classification of the American Heart Association.

On 20 grains a day divided into two doses the concentration in the blood was a little higher, usually between 1.5 and 4.0 mg. per 100 cc., but sometimes rising as high as 5.5 mg. and occasionally falling to low levels. There was no tendency toward accumulation of the drug when administered over a long period of time.

Toxic Symptoms: The daily dose of sulfanilamide taken by our patients was small, and none of the disturbing toxic symptoms which have been observed in patients taking larger doses of sulfanilamide, appeared. Blood counts, urine examinations and determinations of the carbon dioxide combining power of the blood failed to reveal evidence of anemia, renal irritation or acidosis. Cyanosis was not observed. Three patients complained of vertigo when the drug was first given; the symptom disappeared when the dose was reduced and did not recur when it was increased subsequently. Two patients had erythematous eruptions lasting a day or two which could not be definitely correlated with sulfanilamide administration. None of the patients stopped the drug permanently on account of toxic symptoms.

EFFECT OF TREATMENT

Beta Hemolytic Streptococcal Infections: Among the patients receiving sulfanilamide prophylactically there was no instance of an acute beta hemolytic streptococcal sore throat, or other acute infection from that organism throughout the period of treatment. Throat cultures were taken at each visit during 1937–38 and less frequently the preceding winter. During the first winter one patient, and during the second winter four patients, were found with 5 per cent beta hemolytic streptococci in the throat culture during sulfanilamide prophylaxis. In one individual[4] 3 out of 11 cultures were positive; in another, 2 out of 14 cultures. In the other cases a positive culture was found only once. Out of a total of 166 throat cultures taken during treatment, 8 were positive for beta hemolytic streptococci. In none of these cultures was this streptococcus the predominant organism.

[4] This patient had had 40 per cent beta hemolytic streptococci in the throat culture before sulfanilamide was started.

Among the control cases, one patient was hospitalized with an acute beta hemolytic streptococcal infection:

A. M. In April 1937 the patient had an acute sore throat beginning with chills, fever and headache. It was so severe that she was admitted to the Isolation Ward on the fourth day of the disease with temperature of 102° F. and 20,550 leucocytes per cu. mm. of blood; throat culture showed 98 per cent beta hemolytic streptococci. Sulfanilamide 60 grains a day was given, and she was discharged five days later with only one per cent beta hemolytic streptococci in the throat culture.

Ten out of 71 throat cultures taken on the control group were positive for beta hemolytic streptococci, in addition to the positive cultures encountered during major and questionable episodes. Among the positive cultures were two in which the organism represented 50 per cent of the throat flora demonstrated. The percentages of beta hemolytic streptococci in other instances were 30 per cent, 20 per cent, 20 per cent, 12 per cent, 10 per cent, and 5 per cent, respectively.

Thus, there was less evidence of the presence of beta hemolytic streptococci in the treated than in the control cases, but in a few treated cases the organism was present in small numbers.

Sedimentation Rate: The sedimentation rate was determined at every visit by the Wintrobe method (7). The upper limit of normal for the corrected sedimentation rate at the end of an hour by this technique is 10 mm. for both males and females.

In 17 patients the sedimentation rate was normal before and throughout the period of treatment (Table II). (A rare determination lying between 10 and 15 mm. in individuals with otherwise normal sedimentation rates has been disregarded.) In nine patients the sedimentation rate was elevated when treatment was begun and fell to normal during the period of treatment. In seven individuals the sedimentation rate was increased before sulfanilamide was given, and remained elevated throughout the winter. This group includes *G. D.*, who had infected teeth and chronic pelvic inflammatory disease, with elevated sedimentation rate for two winters; *R. d'A.*, who had chronic tonsillitis until tonsillectomy in August 1937; and *J. S.*, who had chronic bronchitis and chronic sinusitis which necessitated drainage. The continued elevation of sedimentation rate of the other four patients in Group 3 was unexplained. Significant fluctua-

tion of the sedimentation rate occurred in three patients; two of these had minor rheumatic episodes (*F. R.*, *M. W.*) and the third had pyelitis (*E. J.*).

Major Rheumatic Episodes: During the months in which the prophylactic treatment was given, not one of the thirty patients receiving sulfanilamide suffered from a major attack of acute rheumatic fever. Seven of the patients received the drug for two successive winters and were free from attacks throughout both seasons. In figure 1, the previous major episodes of rheumatic fever of the 30 individuals receiving sulfanilamide are charted. No attempt has been made to illustrate the severity or duration of the attack, nor the months in which the attack occurred, except to show, during 1936–1938, whether the attack came before, during or after the period of prophylactic treatment.

TABLE II

Sedimentation Rate in Individuals Receiving Sulfanilamide Prophylaxis

GROUP	SEDIMENTATION RATE	1936–1937	1937–1938	TOTAL
1	Normal before and throughout period of treatment	5	12	17
2	Elevated before, fell during period of treatment	6	3	9
3	Elevated before and throughout period of treatment	6	2	8
4	Fluctuated	1	2	3

One patient, *S. R.*, who had received sulfanilamide for two winters, had an attack of polyarthritis and was hospitalized in August 1938, two and a half months after the drug was stopped at the end of the second season.

Between November and June, four of the 30 control patients had five major attacks, three in 1936–37 and two in 1937–38. All of these attacks occurred among the 19 patients who had not undergone sulfanilamide prophylaxis in the previous winter (figs. 1 and 2).

C. A. was on the medical ward with polyarthritis, endocarditis and first degree heart block from December 1936 to February 1937. In May the polyarthritis flared up again, necessitating bed rest at home and treatment in the Cardiac Clinic from May until August 1937.

S. B. was on the medical ward from February to April 1937 with polyarthritis and precordial pain.

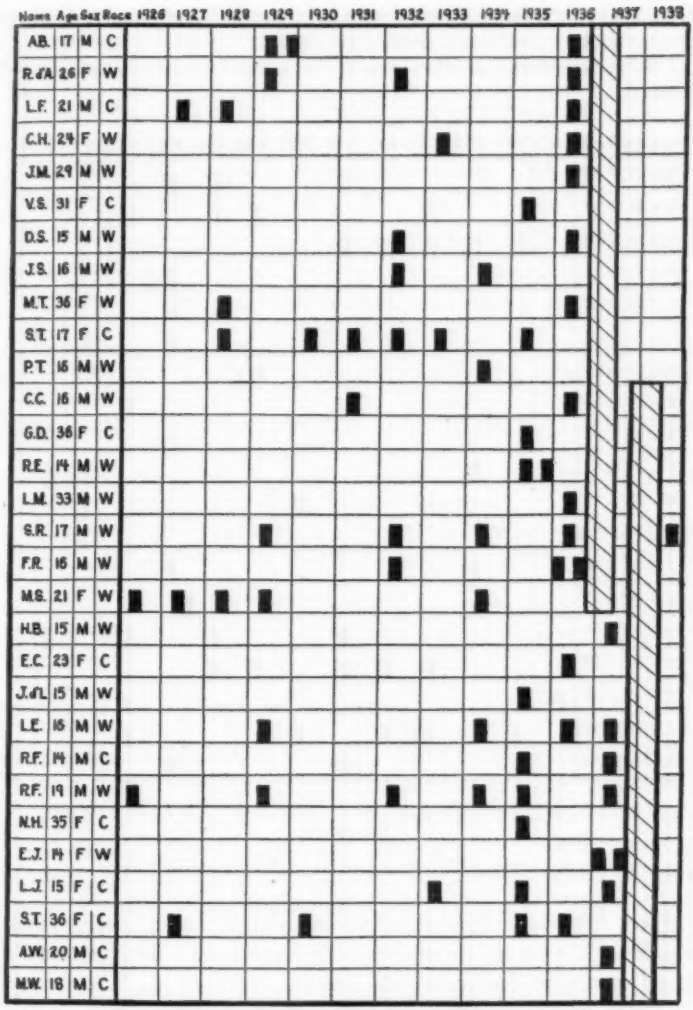
Name Age Sex Race 1926 1927 1928 1929 1930 1931 1932 1933 1934 1935 1936 1937 1938
A.B. 17 M C
R. d'A. 26 F W
L.F. 21 M C
C.H. 24 F W
J.M. 29 M W
V.S. 31 F C
D.S. 15 M W
J.S. 16 M W
M.T. 36 F W
S.T. 17 F C
P.T. 16 M W
C.C. 16 M W
G.D. 36 F C
R.E. 14 M W
L.M. 33 M W
S.R. 17 M W
F.R. 16 M W
M.S. 21 F W
H.B. 15 M W
E.C. 23 F C
J. d'L. 15 M W
L.E. 16 M W
R.F. 14 M C
R.F. 19 M W
N.H. 35 F C
E.J. 14 F W
L.J. 15 F C
S.T. 36 F C
A.W. 20 M C
M.W. 18 M C

FIG. 1. MAJOR EPISODES OF ACUTE RHEUMATIC FEVER IN INDIVIDUALS TAKING SULFANILAMIDE PROPHYLACTICALLY

The crosshatched areas indicate the periods during which the drug was given.

P. L. was on the medical ward during December 1937 and January 1938 with polyarthritis, endocarditis and possibly pericarditis.

M. R. was observed in another hospital during April, May and June 1938 with hemichorea.

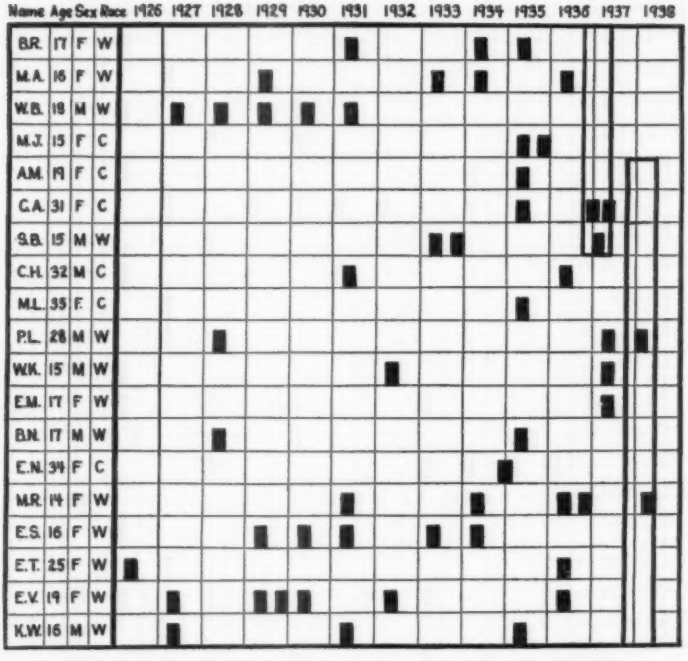

FIG. 2. MAJOR EPISODES OF ACUTE RHEUMATIC FEVER IN CONTROL PATIENTS

Areas enclosed in heavy outline indicate control periods

Minor Rheumatic Episodes: Two individuals had minor rheumatic episodes while receiving prophylactic treatment. Both attacks occurred soon after treatment was begun.

F. R. was started on the small dose of 5 grains daily on November 6, 1936. On November 13, he had an acute rhinitis without sore throat, and a week later his left knee became swollen and sore for three days without other symptoms, but with an elevation of the sedimentation rate which returned to normal in a little

over a month. It should be noted that this patient was not receiving the routine dose of sulfanilamide when the attack developed.

M. W. was started on sulfanilamide 20 grains a day on October 6, 1937. On October 11 he felt ill in school and that night his wrists were painful and hot but not swollen. The next morning the pain was gone and he felt all right. Two days later he had pain in his ankles for a few hours without local heat or swelling. He had no further symptoms, and when next seen in Cardiac Clinic on November 5 his sedimentation rate was normal.

These were the only minor episodes occurring while sulfanilamide was being given.

In the control group, two minor attacks occurred as follows:

P. L. came to the Accident Room on February 17, 1938 complaining of an abscessed tooth, which was extracted the following day. On February 19 he had pains in his finger joints, and from February 25 to March 4 he had sore, swollen knees and right wrist and the sedimentation rate rose from 2 to 27 mm. He had not received sulfanilamide from us prophylactically but he was given 40 grains a day of the drug by another physician at the time of the dental extraction, from February 17 to 19, and half this amount for two days more.

E. M. had been on the medical ward with acute rheumatic fever, polyarthritis, myocarditis and skin lesions resembling urticaria or erythema multiforme from January to April 1937. In March 1938 she began to have skin lesions even more severely, which continued until July. While the lesions, according to the patient's description, suggested giant urticaria, the lesions seen in the Cardiac Clinic were typical of erythema marginatum. In June 1938 she was in bed with fever and sore throat for several days, and throughout the period of skin eruption she had polyarthralgia and occasional precordial pain.

The cases of F. R., M. W. and P. L. offer slight evidence that sulfanilamide may be without prophylactic value if administration is begun less than two weeks before the onset of a rheumatic episode.

Questionable Rheumatic Episodes: None of the patients receiving treatment had any febrile or incapacitating illness in which the diagnosis of rheumatic fever was brought into question. (Two patients had clinically typical influenza with leucopenia.) Among the control patients, three had illnesses requiring hospitalization, in which a relationship with the rheumatic cycle was possible but not certain:

J. S., who has mitral stenosis, entered the medical ward on October 12, 1937 with broncho-pneumonia. His sedimentation rate, which had been normal in August and was 15 mm. on October 8 when he first complained of an upper respiratory infection, rose to 32 mm. on October 16, had fallen to 16 mm. on discharge on

November 2 and was normal November 16. Sputum culture showed a mixture of organisms including pneumococcus type IX in small quantity; no beta hemolytic streptococci were cultured from throat or sputum. There were no other signs of rheumatic activity. In 1934 he had had a similar attack with more fever and beta hemolytic streptococci present in his throat.

C. A., who has mitral stenosis and first degree heart block, had two attacks of polyarthritis in the spring of 1937. In the spring of 1938 she complained of feverishness, weakness and joint pains. On May 17, 1938 she was admitted to the medical wards with fever, swollen knee and ankle joints, tender swollen lower legs with increased redness and local heat and several subcutaneous nodules, tender swelling of a synovial bursa on the back of her left hand and a fine papular rash which itched and had been present three weeks. Sedimentation rate was 32 mm.; throat culture showed 10 per cent beta hemolytic streptococci. The blood Wassermann which had been negative the year before was positive. She remained on the ward five weeks, receiving antisyphilitic treatment and also, for four weeks,

TABLE III

Incidence of Isolated Rheumatic Symptoms in Individuals Receiving Sulfanilamide Prophylaxis

SYMPTOM	1936–1937	1937–1938
Symptom free	8	10
Occasional mild arthralgia	6	5
Epistaxis	3	2
Slight sore throat	2	1
Occasional precordial pain	0	1

large doses of salicylates. It was never fully determined whether this attack represented secondary syphilis alone, or rheumatic fever or both. The leg lesions were suggestive of an erysipeloid infection, but cleared up quickly.

L. F., who has mitral insufficiency and stenosis and aortic insufficiency, began to have sharp abdominal pain, substernal and precordial pain with some dyspnoea early in December 1937. On January 3, 1938 he was admitted to another hospital with totally irregular cardiac rhythm at a rate of 140, slight orthopnoea, but no other signs of congestive failure. This was the patient's first attack of auricular fibrillation. His heart reverted to normal sinus rhythm with first degree heart block after a course of digitalis and quinidine, and he left the hospital January 30.

At each visit the patients were specifically questioned concerning the occurrence of epistaxis, joint pains, sore throat, rash, nausea, vomiting, precordial pain, twitching or other rheumatic symptoms. Among the treated group isolated symptoms were noted as shown in Table III. These symptoms were all mild. The arthralgia was gen-

erally described as "occasional aching in my shoulder (or knees)." The control group were questioned at less frequent intervals, so that accurate records of these isolated symptoms could not be kept on the entire group, but they were subject to much the same type of symptoms, except that sore throats with colds seemed more frequent, and epistaxes were more pronounced.

SUMMARY

Sulfanilamide was given continuously during the course of two winters to 30 individuals with a recent history of acute rheumatic fever. The drug was taken daily over a seven months' period in a dosage of 15 to 20 grains without ill effects. None of the patients had a major attack of acute rheumatic fever or an acute beta hemolytic streptococcal infection while taking sulfanilamide. Of 30 control patients, four developed five major attacks of rheumatic fever during the same period, one was hospitalized because of an acute beta hemolytic streptococcal infection and three others had acute illnesses which might have been of a rheumatic character. It is recognized that the group studied is too small to permit definite conclusions concerning the efficacy of sulfanilamide in preventing attacks of acute rheumatic fever, but our results are encouraging and warrant further studies along this line.

The sulfanilamide used in these investigations was supplied by the Winthrop Chemical Co., Inc., New York City.

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BOOK REVIEWS

(The reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

The Practice of Urology. By LEON HERMAN. 923 pp. Illus. $10.00. (*W. B. Saunders Co., Philadelphia, 1938.*)

This is a record largely of the author's own clinical experience. It should serve as a remarkable source book of interesting cases concisely reported. The wealth of new material is impressive.

The sections on symptomatology and diagnosis throughout the book are splendidly done. Cases are well illustrated by x-ray reproductions, diagrams and photographs of pathological specimens. Photomicrographs are conspicuously lacking; there are but five in the entire volume.

In the sections on prognosis and treatment, the author has expressed his opinions freely and characteristically. Adequate reports from the literature and opinions from other writers are incorporated, but Dr. Herman's conclusions are unmistakable, and they are stimulating, whether one agrees with them or not.

Operative technique, with the exception of transurethral and cystoscopic methods, has apparently been purposely omitted.

Parts one and two on diagnosis and instrumental therapeutics are well presented for the beginner in urology.

Part three on the kidney is complete. It includes a large number of case reports with remarkable illustrations of congenital abnormalities. Traumatic conditions are adequately treated. Cysts receive especial emphasis. The fascinating subject of hydronephrosis is thoroughly presented. Primary (congenital) and secondary (acquired) hydronephrosis are discussed separately after a splendid outline. The sections on tumors and infections contain many very interesting case records.

The subject of gonorrhoea is fully and admirably presented.

In brief, this is more than another textbook. It incorporates the author's great clinical experience and is especially recommended to the student and practitioner of urology.

L. G. L.

The Diagnosis and Treatment of Sexual Disorders in the Male and Female. By MAX HUHNER. 490 pp. $5.00. (*F. A. Davis Company, Philadelphia, 1937.*)

A review of a subject by a man of wide experience is always valuable. In this volume the author apparently relies a great deal on reveries to recall many important points. Evidently more experienced in male urology than in gynecol-

ogy, he attempts to deal with such subjects as sterility, impotence, masturbation, frigidity and dyspareunia in both sexes with equal facility. The book is crowded with repetition and the conclusions are frequently misleading, particularly those relating to the female.

The chapters dealing with *coitus interruptus* and continence are the most outstanding. In discussing the latter, however, after presenting both sides of a subject much in dispute, the conclusions reached are extremely unconvincing.

There is quite an extensive bibliography. Many of the articles listed, the author has apparently not digested, for the information contained in them is not incorporated into his discussion of the subject. For instance, when he advises that artificial insemination be done just after the cessation of the menstrual period he displays little insight into the present conception of the time of ovulation. Again, on page eighty-one he states that there is no method to determine whether or not ovulation has occurred, while in the bibliography he lists several articles on this subject.

Generally, however, the author treats a difficult and much neglected subject in an interesting, readable and scholarly manner. His book should be added to the small list of available comprehensive works on sexual disorders, which may be recommended to both student and clinician.

J. H. L.

Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN. 7th ed. 319 pp. Illus. $3.00. (*Paul B. Hoeber, New York, 1938.*)

This is a very useful little book. It contains brief but adequate descriptions of all the methods employed in the examination of the nervous system including not only the conventional clinical tests, but also some discussion of intelligence tests, psychiatric investigation, interpretation of X-ray pictures of the skull, ventriculography, encephalography and electrical examinations. The writer is of course a well known and experienced neurologist and it is the mature judgment with which the book is written that makes it valuable. One finds not only a list of diagnostic procedures but a sound evaluation of their significance and a clear idea of the proper indications for their performance. In this 7th edition new material and a number of new illustrations have been added so that the book is well up to date.

F. R. F.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By FRANK R. FORD, M.D. 953 pp. Illus. $8.50. Charles C. Thomas, Springfield, Illinois, 1937.

The traditional neurologist, whose daily experience is confined to the Neurological Clinic or practice in his specialty, works at great disadvantage. Though he sees numbers of patients suffering from a variety of neurological disorders and gets to know the rarities, and though he may have special facilities for clinical study, he suffers badly from isolation. He lacks the opportunity to see disease

of the nervous system at the beginning. Patients come to him ticketed, if not already labelled. He does not encounter the various disorders which occupy the borderline region between classical neurology and general medicine. Though he consults with the internist, ophthalmologist, surgeon or pediatrician, it is in a formal way. He does not work shoulder to shoulder with them, so to speak, and above all remains out of touch with their everyday thought and the methods of investigation furnished by biochemistry and immunology. His essential function has been to elicit symptoms and refer them to the anatomical part in the brain or spinal cord giving them origin. At this game of anatomical localization he has become extraordinarily proficient. We do not wish to belittle the contribution of the neurologist to knowledge concerning functions of the nervous system or to improvement of diagnosis, but the real hope for progress in disease of the nervous system, as of other parts of the body, lies in the development of understanding of the chemical nature of the pathological processes at work. Neurology ought not to be separated from general medicine. Specialists in neurology will always have their place but they should be primarily internists with special concentration on disease of the central nervous system.

Dr. Ford has had the enviable opportunity of having been for a number of years the roving neurologist of a large hospital and medical school. Although he is a member of the Department of Internal Medicine he has worked in close association with the members of other departments. For a long time he has been allured by the problems arising from disease of the central nervous system in infants and children, because as a whole they differ so much from those seen in adults, and are so poorly understood.

The book which Dr. Ford has written is a little less than 1,000 pages long. It contains many excellent illustrations. The discussion of each main topic is followed by a bibliography including the more recent articles. A glance at the table of contents is sufficient to show the completeness of the book. Certainly no experience which a neurologist might have is omitted from discussion.

The exposition of the principles of neurological diagnosis and its anatomic substratum with special reference to the child are dealt with in the first 150 pages. Especially useful subjects presented in this introductory part are the methods of x-ray examination of the brain with the use of air, and the discussion of the embryology, morphology and clinical physiology of the immature nervous system. The treatment of the classical diseases of the central nervous system, those which fill the ordinary textbooks of neurology, is all that could be desired. For example, the presentation of the prenatal diseases of the nervous system is the best that we know anywhere. The heredofamilial and degenerative diseases of the nervous system are dealt with from large experience and knowledge. The discussion of the toxic, metabolic and circulatory disorders is particularly fine. The chapter on neoplasms of the nervous system and related conditions epitomizes a large, unusually controlled experience. The presentation in sequence of the various diseases of the autonomic system is an unusual feature. In the final chapter Dr. Ford discusses the possible etiologic and pathologic conditions which may produce some of the well known symptom complexes.

A particular feature of the book, as already hinted, is the inclusion of descriptions and discussions of various disorders of the nervous system which are borderline between those of classical neurology and general medicine, the disorders so commonly seen by the internist and so rarely by the neurologist. The pages are full of examples: invasion of the nervous system by *actinomyces* and other molds, torula meningitis, tick-bite fever, malaria, trichiniasis, icterus gravis neonatorum with kern icterus, cerebral complications of acute glomerular nephritis, hyperparathyroidism and juvenile Paget's disease, hypoglycemia, insulin shock, etc. It is most useful to have a book which presents so much of general medicine written from the standpoint of neurology.

The book is clearly and concisely written. Irrelevant matter will not be found. Fancies and hypotheses are given their proper place, and facts their just values. This is the work of a true scholar with finely developed critical judgment. There is something about it which inspires confidence. The author has succeeded, so far as is ever possible, in transferring his own experience to that of the reader. This is the goal of all textbooks.

The writer does not know any work on neurology in or outside childhood which compares with Dr. Ford's either in scholarship, scope or practical usefulness. It is one of the best additions to the literature on diseases of children which has been made in a long time.

E. A. P.

BOOKS RECEIVED FOR REVIEW

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Vitamin B_1 and its Use in Medicine. By ROBERT R. WILLIAMS and TOM DOUGLAS SPIES. 411 pp. $5.00. The Macmillan Company, New York, 1938. (Macmillan Medical Monographs)

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Laboratory Manual of Hematologic Technic. By REGENA COOK BECK. 389 pp. Illus. $4.00. W. B. Saunders Company, Philadelphia, 1938.

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Surgical Pathology. By WILLIAM BOYD. 4th ed. revised. 886 pp. Illus. $10.00. W. B. Saunders Company, Philadelphia, 1938.

Ueber die Beziehungen der Qualität des Nahrungseiweisses zum Ablauf des Betriebsstoffwechsels. By ADOLF BICKEL. 100 pp. Paper bound 10 Swiss francs. Benno Schwabe & Co., Basel, 1938.

Outline of Roentgen Diagnosis. By LEO G. RIGLER. Atlas edition, 212 pp. + 254 illus. $6.50. J. B. Lippincott Co., Philadelphia, 1938.

Pathological Technique. By FRANK BURR MALLORY. 434 pp. Illus. $4.50. W. B. Saunders Co., Philadelphia, 1938.

Textbook of Nursing Practice. By HESTER K. FREDERICK and ETHEL NORTHAM. 2nd ed. revised. 418 pp. Illus. $3.00. The Macmillan Company, New York, 1938.

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Anus, Rectum, Sigmoid Colon. By HARRY ELLICOTT BACON. 855 pp. Illus. $8.50. J. B. Lippincott Company, Philadelphia, 1938.

Cancer—with special reference to cancer of the breast. By R. J. BEHAN. 844 pp. Illus. $10.00. C. V. Mosby Company, St. Louis, 1938.

Osler's Principles and Practice of Medicine. 13th ed. Revised by HENRY A. CHRISTIAN. 1424 pp. $9.00. D. Appleton-Century Company, New York, 1938.